



NIH Research Plan

FY 1986

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes
of Health

NATIONAL INSTITUTES OF HEALTH
RESEARCH PLAN
FY 1986

June 1984

(For Administrative Use)

TABLE OF CONTENTS

INTRODUCTION	1
SECTION I--Selected Areas of Scientific Opportunity.	5
A. Genetics	9
B. Immunology	17
C. Neuroscience	23
D. Instrumentation.	27
SECTION II--The NIH Planning Function.	33
SECTION III--Selected Policy Considerations.	51
A. Research Infrastructure.	55
1. Extramural Construction.	55
2. Research Instrumentation	58
B. Research Training.	61
C. The Care and Use of Animals in Research.	67
D. The NIH Organizational Structure	73
E. NIH/Industry Interaction	81
SECTION IV--Summary of BID Program Opportunities	87
National Institute on Aging (NIA).	89
National Institute of Allergy and Infectious Diseases (NIAID).	103
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK)	111
National Cancer Institute (NCI).	127
National Institute of Child Health and Human Development (NICHD).	147

National Institute of Dental Research (NIDR)	157
National Institute of Environmental Health Sciences (NIEHS).	171
National Eye Institute (NEI)	177
National Institute of General Medical Sciences (NIGMS)	189
National Heart, Lung, and Blood Institute (NHLBI).	193
National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).	213
Division of Research Resources (DRR)	225
John E. Fogarty International Center (FIC)	247
National Library of Medicine (NLM)	255
Division of Computer Research and Technology (DCRT).	265

INTRODUCTION

INTRODUCTION

The overriding objective of the NIH during current periods of fiscal constraint is to maintain the strength of the biomedical research enterprise in order to sustain the substantial rate of progress that has been achieved in advancing knowledge in the biological and behavioral sciences and to capitalize on the many scientific opportunities presented by these recent research accomplishments.

Recent developments have made it clear that the boundaries between traditional scientific disciplines have in many cases become almost indistinguishable as inquiry proceeds at the molecular level of organization. Similarly, the link between basic science and technology has become more immediate, and in many important areas of biomedical research the two are, in fact, inextricably bound in a mutually reinforcing and synergistic relationship unprecedented in the history of biomedicine.

Section I describes developments in several broad areas of science and technology--genetics, immunology, neurosciences, and instrumentation--which, by virtue of exceptional past accomplishments, hold significant promise for future progress.

Section II provides a description of the broad set of activities which comprise the planning function in the Office of the Director (OD), NIH.

Section III discusses some of the areas of current concern that must be considered in the planning and conduct of NIH programs. These include such concerns as: (1) the need to address the growing problem of deterioration and obsolescence of research laboratories and instruments, (2) the adequacy of the NIH organizational structure in responding to changing demands, (3) the care of animals used in research, (4) the need to provide adequate incentives for research training, and (5) the promotion of fruitful government/industry relationships in health research.

Section IV discusses new initiatives and major program changes planned for FY 1986, and describes the specific scientific opportunities that will be pursued. These discussions were predicated on funding assumptions operating at the time the plans were developed and are subject to modification to reflect changes which may occur during the actual development of the FY 1986 budget.

SECTION I--SELECTED AREAS OF SCIENTIFIC OPPORTUNITY

SELECTED AREAS OF SCIENTIFIC OPPORTUNITY

During the past few decades the biological sciences have been transformed through an explosion of new knowledge. Fundamental discoveries have occurred at a prodigious rate, large confluences of knowledge have given rise to entirely new disciplines, and a research capability has evolved with a depth and sophistication to rival that which was achieved earlier in the physical sciences.

While this revolution has affected virtually all areas of biomedical research, the fields of genetics, immunology, and neuroscience have become especially prominent by virtue of the potentially broad repercussions of recent breakthroughs in these areas. And this progress has been greatly enhanced by recent developments in instrumentation.

The following discussion is intended merely to convey the sweep of this progress and to provide a few examples of significant discoveries that have contributed to that progress.

Genetics

Genetics, that branch of biology which deals with heredity and variation, encompasses a broad scope of topics including: (1) identification of the hereditary material and the nature of its chemical and structural properties; (2) study of the organization of genes into chromosomes and the transmission of the chromosomes from parents to progeny; (3) analysis of the interactions of the different genes and the role of the environment or other influences in producing the characteristics of the individual; and, (4) study of the different types of genetic diversity that can occur and the consequences of this diversity to the individual and to the population.

The study of genetics traditionally begins with consideration of the work of Gregor Mendel and the principles of inheritance that he proposed in 1865. Working with various strains of peas, Mendel postulated the existence of pairs of factors, now called genes, that controlled traits such as seed shape and color, pod shape and stem length. Results from his breeding experiments led him to believe that each parent plant contributed one factor from each pair which were passed on to the next generation independently.

Hereditary transmission via the sperm and egg became known by 1860, and in 1868 Haeckel, noting that sperm consisted mostly of nuclear material, postulated that the nucleus was responsible for heredity. Almost twenty years passed before chromosomes were singled out from other components of the nucleus as the active hereditary factors. Mendel's work was ignored until 1900, largely because the rules for chromosome behavior during fertilization and cell division were not yet understood.

Identification of Genetic Material

Nucleic acids (DNA and RNA) were discovered in 1869, but their importance as the material that carries genetic information from one generation to the next was not proved until 1944. Avery, MacLeod and McCarty showed that nucleic acids rather than proteins were responsible for transmitting heritable traits. In 1947, Edwin Chargaff chemically analyzed the DNA isolated from various organisms and found that the nucleotides (thymine, cytosine, adenine and guanine), exist in specific proportions, that is, for every thymine, there is one adenine and for each guanine, there is one cytosine. The fact that this one-to-one ratio held constant over species boundaries was remarkable but unexplainable.

Structure of DNA

The account of James Watson and Francis Crick's development of a model for the structure of DNA is now a classic both in the scientific and popular literature. One of the reasons the story is so fascinating is that it provides the public with a rare glimpse into the highly competitive environment from which scientific discoveries arise. Although there was some skepticism surrounding Avery's conclusion, scientists from several laboratories began to focus on DNA as the key to divulging the "secret of life."

The predictable ratios of nucleotides observed by Chargaff suggested an inherent regularity in the DNA molecule which led at least one prominent researcher down the wrong path. Based on the helical configuration of certain proteins, Linus Pauling presented a structure which was quickly disputed. Important clues provided by two scientists at King's College, London, so provoked Watson's imagination that he left his postdoctoral studies in Copenhagen and went to work at the Cavendish Laboratories in Cambridge. There, he met Francis Crick, a physicist who was using X-ray diffraction techniques to interpret protein structures. These same techniques were applied to the DNA problem by Maurice Wilkins and Rosalind Franklin. They placed DNA crystals in the path of X-rays and photographed the pattern of diffraction created by the beam's interaction with the DNA atoms.

Wilkins and Franklin recognized the probable helical nature of DNA and discussed these findings at a meeting Watson attended in Italy. However, Watson and Crick worked with wire and brass models for over a year before they proposed a molecular structure for DNA. Their solution, that DNA is a twin helical chain coiled about a single axis, was published in Nature, on April 25, 1953.

Confirmation of a molecular model often comes from the relationship between the structure and its function. If the model answers questions about how the molecule carries its biochemical duties, its credibility is significantly enhanced. Hereditary material has two critical responsibilities: first, in order to provide the service of carrying genetic information from one generation to the next, DNA must be capable of duplicating itself; and second, it must be capable of directing the formation of all the other structures of the organism, particularly structural proteins and enzymes. Enzymes are proteins which are responsible for coordinating the metabolic functions of the organism. The relationship between the structure of DNA and its cellular functions will be addressed in the next section.

Structure and Function of Genetic Material

The backbone of each nucleic acid strand is made up of phosphates and pentose sugars, while the nucleotide bases project between them as bars and hold the two chains of the double helix together by means of chemical linkages known as hydrogen bonds. Results from Chargaff's earlier chemical analyses can be explained by the fact that the nucleotides must join to form specific pairs, that is, adenine can form hydrogen bonds with only thymine, and cytosine can bond with guanine in DNA, or with uracil in RNA molecules. Hydrogen bonds are not very strong and abnormal pairings are generally unstable enough to prohibit their formation. However, occasionally these errors can occur resulting in an aberrant protein product.

The beauty of the double helical structure was that it immediately suggested a method by which DNA could replicate itself. When the hydrogen bonds between base pairs break, the helix splits open like a zipper, so that one strand can serve as a template upon which a new complementary strand forms. After determining the chemical components that make up genetic material and a method for its duplication, the next step was to explain how the single strand of DNA instructs the cell to form proteins.

Protein synthesis is a more complicated procedure than simple DNA replication and, in fact, can take place in the absence of DNA. This indicates that an intermediate template carries genetic information to the cytoplasmic sites of synthesis. This template is RNA, which is formed by transcription of DNA in a manner similar to DNA replication. The single strand of RNA is then translated into protein by providing a guide for the formation of a chain of amino acids. The twenty amino acids are the links in the protein chains. The length of the chain and sequence of amino acids identifies the specific protein. The next section describes how the nucleotide sequence dictates which amino acid will be added to the last one until translation is halted and a new protein is produced.

The Breaking of the Code

The four nucleotides are often referred to as the letters of an alphabet which spells out the sequences of amino acids in the various proteins of the body. The group of nucleotides that specifies one amino acid is called a codon. The simplest possible code would be one nucleotide for each amino acid but then there could only be a total of four amino acids. If the code were based on doublets, there could be only sixteen amino acids. Experimental evidence provided by Francis Crick in 1961 confirmed the theory that each codon was made up of three bases which allowed for sixty-four possible sequences. This means that there is enough leeway in the alphabet to spell some additional words, such as commands to start and stop DNA transcription.

The major problem is: Which three-letter word codes for which of the 20 amino acids that are incorporated into protein chains? Proteins come in many sizes, from three amino acids in length to several hundred. Chromosomes are made up of DNA but RNA, which is present in quantities two to eight times that of DNA, is found in several forms at various sites in the cell. Attempts to match a DNA sequence with its corresponding amino acid sequence began with investigation of a simple system, the single-cell bacterium, *Escherichia coli* or *E. coli*.

A quick look at the data would discourage the most eager efforts to break the genetic code. One *E. coli* contains the genes for approximately 3,000 proteins that are synthesized on 15,000 ribosomes. Each *E. coli* may contain only a few copies of one protein but 15,000 of another. Obviously, even the lowly bacterium is too complex. Marshall Nirenberg, an intramural NIH scientist, developed a technique which allowed him to manipulate enough components so that he was able to isolate the precise variable that provided the key to the genetic code.

Nirenberg essentially set up a factory with all the necessary materials a cell would use to make proteins with the exception of one critical element, the messenger RNA that dictates which amino acid should be attached next. Instead, he added synthetic RNA whose nucleotide sequence was known and then watched to see which radioactively labelled amino acid was chosen. When a string of adenines representing an A-A-A codon was fed into the protein factory, only one amino acid, lysine, was incorporated. Similarly, U-U-U was found to code for phenylalanine. By such experiments, Nirenberg's and S. Ochoa's laboratories quickly succeeded in identifying the nucleotide composition of some 50 code words for the various amino acids. All but three of the 64 words were found to code for amino acids, these three are used to terminate transcription. These efforts lead to a Nobel Prize in 1968.

The most amazing quality of the genetic code is its universality, that is, A-A-A codes for lysine in humans as well as in giraffes. Of the estimated 100,000 genes found in a human cell, over 800 have been located on their respective chromosomes and new genes are being mapped at a rate of more than 200 per year. Even so, the amino acid sequences of only two percent of the 50,000 proteins produced in the body have been identified.

Deciphering the genetic alphabet coding for specific amino acids that in turn spell out an entire protein, seemed to tie up all the loose ends in explaining how DNA carries genetic information. Although it was known that mutations could and do occur, and that pieces of chromosomes might break off and attach elsewhere, the common view was that genetic material was generally stable. However, we now know that pieces of DNA can move from one part of a chromosome to another and even between chromosomes.

In 1983, Barbara McClintock was awarded the Nobel Prize for her discovery of these segments, known as transposons, or "jumping genes." This discovery made it possible to "map genes," or to determine the relative positions of specific genes on their chromosomes. However, until 1976, genetic mapping was an extremely laborious procedure. Efforts to decipher the sequences that coded for specific proteins were hampered by the inability to gather enough copies of one gene to provide sufficient material for sequential analysis. The discovery that made this possible triggered a biological revolution.

Recombinant DNA

Attempts to solve a seemingly unrelated problem provided the answer to years of frustration. Just like people, bacteria are subject to viral infection, however, the bacteria have developed a defense mechanism that is quite a bit more aggressive than bed rest and fluids. Bacteria secrete an enzyme that is capable of slicing viral DNA into pieces. Scientists studying these bacterial weapons, called restriction enzymes, made two critically significant observations: (1) the enzymes from any one strain of bacteria always clipped the viral DNA at the same places, resulting in identical fragments time after time; and (2) enzymes from different strains of bacteria make their cuts at different places. Therefore, by cleverly applying both of these tools, it was possible to extract the DNA from a large number of cells and snip it up so that large quantities of identical sequences of DNA could be isolated.

The next battle in the genetic revolution won the war. In 1973, scientists learned how to insert these fragments of DNA into the genome of a normal bacterium so that when it replicated itself, it also made copies of the inserted DNA. Bacteria reproduce so quickly that they represent a factory working double shifts, round-the-clock, cranking out DNA. Given the proper building materials, they will construct the proteins coded by the fragments of DNA thus giving away the secret. The new field of biotechnology is based on the ability to induce bacteria to make enormous quantities of one pure protein at much less expense than it would take to isolate the product from its natural source, or to synthesize it by chemical means.

Gene Regulation

Gene mapping facilitated efforts to determine the mechanisms that controlled the expression of each gene. What signal told the cell to begin production of a needed protein, or when enough had been made? The operon theory of regulation of genetic expression was put forward in the late 50's based on studies of amino acid-dependent mutant strains of bacteria. By monitoring the production of certain enzymes, it was possible to trace the activity of the genes that coded for production of that enzyme, and observe other changes in the organism's metabolism. These experiments uncovered a sort of amplification system--when one gene is turned on, adjacent genes are turned on simultaneously. If the operon gene is susceptible to mutagenic factors in the environment such as viruses, chemicals or radiation, normal growth control mechanisms may be disrupted. In some cases, this may lead to cancer.

Oncogenes

As mentioned earlier, within the normal human genome there are sequences that are susceptible to activation by a variety of external factors. Once activated, these sequences acquire the ability to transform other cells and form tumors. These sequences are called oncogenes and their discovery has opened a new area in the study of cancer prevention and control. Understanding of the factors that can activate oncogenes--environmental, viral, chemical--and the mechanisms by which they work will likely have a major impact in clinical medicine within the foreseeable future. Indeed, scientists recently found that one virus known to be present in a high percentage of persons with T cell leukemia, is also closely related to another virus that may be responsible for Acquired Immune Deficiency Syndrome.

Genetic Diseases

There are more than 3,000 genetic diseases to which man is susceptible. When a gene is damaged, it may no longer be capable of carrying out its function of coding for a particular protein at all, or the product may be aberrant. In general, damage to a gene results in a defect in its gene product, the corresponding protein. If this sequence of events leads to pathologic symptoms, and it often does, we have a genetic disease. Elucidation of the biochemical defects that underlie a variety of such diseases is a goal pursued by many scientists working with tools developed only recently.

Often the protein in question is an enzyme. If the enzyme is absent, then the reaction catalyzed by that enzyme cannot go forward and the desired product will not be formed. Signs and symptoms of disease will occur if the protein product is essential, or if the elevated levels of the precursor prove to be toxic. Another consequence might be the accumulation of the precursor to that reaction in the body, often causing toxic effects. Other genetic diseases are associated with the production of crippled proteins such as the globins that may occur in hemoglobinopathies such as sickle cell disease.

Although many genetic diseases are quite rare, more are being discovered as diagnostic techniques become more sophisticated. For this reason, the genetic diseases taken together have a considerable impact on public health expenditures, and have been estimated to account for approximately one quarter of all pediatric admissions to hospitals.

Not all genetic diseases are rare. In fact, one genetic defect is common to all Homo sapiens, as well as to guinea pigs. All other animals are able to make an enzyme that metabolizes gulonolactone to ascorbic acid. That is, each cell should have the ability to produce its own vitamin C. Instead, all humans have scurvy, the disease that results from ascorbic acid deficiency. Unless their diets are supplemented with fresh fruits and vegetables that are rich in vitamin C, people are subject to a very serious condition. Scurvy is not usually looked upon as the genetic defect that it is unless it is recognized that a mutation occurred somewhere in our phylogenetic past, resulting in the loss of a gene responsible for a certain enzyme.

The day when genetic defects may be corrected, rather than treated symptomatically, is approaching. The first experiments designed to correct a single gene defect are under way. Patients who lack the gene that codes for the enzyme HGPRT have a devastating disease known as Lesch-Nyhan syndrome. If the appropriate gene can be introduced into the genome of Lesch-Nyhan patients, symptoms such as crippling palsy, retardation, gout and a compulsion to bite themselves might be averted.

Identification of the genes that are responsible for certain diseases that appear in midlife might be made at birth. Such diseases include diabetes, allergies, peptic ulcers and other common afflictions of midlife whose onset might be prevented with early diagnosis.

The practice of genetic counseling is becoming less a matter of statistical probabilities and more scientific certainties. As more DNA markers for familial diseases are located, the precision of genetic screening for inherited disorders increases. The role of genetic counselors is now more proactive with the positive identification of carriers of genetic disorders.

The ability to map genes, to determine which chromosomes bear the genes for making specific proteins that have structural or enzymatic functions, has opened the door to a host of new techniques. In some cases, diagnosis of inherited diseases, can now be made prenatally, enabling physicians to initiate treatment for certain disorders in utero. For example, enzyme deficiencies that can cause progressive damage may be ameliorated by early dietary changes.

The field of genetics is undergoing a period of unprecedented growth whose effects are spread over several areas of basic science as well as the practice of medicine. New techniques in DNA sequencing and manipulation have led to a greater understanding of how environmental factors influence gene function. This understanding, in turn, promotes progress in the diagnosis, prevention and treatment of a wide variety of genetic and other diseases, such as cancer, heart disease, schizophrenia, diabetes and hypertension. Advances

in genetics are shedding new light on how the body reacts to virus infections and why individuals react differently to some drugs. There are growing implications for such fundamental questions as how people grow and what happens during aging. The speed with which hopes are becoming reality promises more of the same for the future.

Immunology

Immune Response

The study of immunity is properly the study of resistance to infection. Resistance is a complex state arising from properties of the individual, of the community and of the species. However, immunity's most remarkable feature is the specific nature of its enhancement in individuals after recovery from a specific infection. From the earliest stage of its development, the field of clinical bacteriology gave pre-eminence to the study of this acquired specific resistance to invasion by microorganisms as a powerful means of acquiring protection. It followed that antigenic stimulation and antibody production began to be investigated in the context of infectious disease and induced immunity to it.

In the early part of this century, scientists realized that the immune system could produce unpleasant and sometimes dangerous hypersensitivity to subsequent exposure to the stimulating antigen, even without conferring resistance. Researchers quickly learned that the phenomenon of resistance that had first attracted their attention, was not even central to the function of the immune system. Some bacterial infections induced antibodies that had no protective value whatsoever. Furthermore, specific antibodies and even hypersensitivity could be evoked by exposure to harmless substances, from which no protection was needed. An example of this phenomenon is the allergic response some individuals experience when exposed to pollen, dust, fur or other particulates.

Discovery of its frailties provoked efforts to understand the immune system more thoroughly, in order to leash and modify its activity. One of the major biomedical advances in the last decade was the identification of substances that are able to regulate immunity and may, under adverse conditions, cause inflammation and tissue destruction. The field of immunopharmacology includes the development of drugs that can ameliorate the ill effects of over-zealous components of the immune system, thus offering some relief from allergic and immunologic diseases. Efforts to understand the mechanisms that exert control in a natural setting may lead to our ability to manipulate the immune system in order to deflect adverse immune responses that produce these and other diseases.

Infections, the most common human diseases, are responsible for nearly 25 percent of all visits to physicians each year. For children, this figure is 65 percent. Generally, however, in spite of frequent exposure to infectious agents, we do not become ill, and when we do, tend to recover quickly.

The body's "natural" protection is the function of the immune system, a complex network of specialized organs and cells that has evolved to defend the body against attacks by "foreign" invaders. The immune system, similar in complexity to the intricacies of the brain and nervous system, displays several remarkable features. It can distinguish between "self" and "nonself." It is able to remember previous experiences, and to react accordingly; that

is, protection is provided against repeat infections of certain diseases such as measles and mumps. Of the millions of molecules that are determined to be "nonself," many are newly synthesized compounds whose structures could never have been predicted and prepared for, but are nevertheless recognized and attacked by the weapons employed by the immune system.

Antigens are "nonself" or foreign molecules that can trigger an immune response when they are introduced into the body. An antigen can be a virus, a bacterium, a fungus or a parasite, or even a portion or product of one of these organisms. The immune system also reacts to tissue antigens from another individual, as in a transplant or blood transfusion.

Components of the Immune System

Although not often thought of as such, the immune system is really an organ system. The success of this system depends upon a dynamic and elaborate regulatory communications network. Stationed throughout the body are the "lymphoid" organs, so called because they are concerned with the growth, development and deployment of lymphocytes, the white blood cells that are the primary operatives of the defense network. The one trillion lymphocytes operate in harmony, each set and subset of cells performing its part in the system of checks and balances that regulate immune processes. Immunologic disease results when one component fails and an imbalance develops. Acquired immune deficiency syndrome (AIDS), for instance, is characterized by the absence or decreased levels of one set of lymphocytes and elevated presence of another. Lymphoid organs include the bone marrow, thymus, lymph nodes, spleen, tonsils, appendix, as well as clumps of lymphoid tissue dispersed in the wall of the small intestine known as Peyer's patches.

Lymphocytes

In 1961, J.F.A.P. Miller first showed that lymphocytes, which look homogeneous under the microscope, are not all the same, but actually comprise two major classes with many different subsets. The B cells (named for bursa of Fabricius, or bone marrow in chickens) attack invaders by producing soluble antibodies which circulate in the blood and interact with antigens, frequently macromolecules associated with bacterial and viral invaders. The T cells (named for the thymus which orchestrates their function) have a variety of jobs and titles to match, such as helper, suppressor, and killer cells. The helper cells activate B cells and other T cells, while the suppressor cells can turn them off. Natural killer cells are large granular lymphocytes. As their name implies, they attack and destroy other cells.

At different stages in their maturation process, T cells are receptive to messages they get by passing through the thymus directly, or by being activated by circulating thymic hormones. The mechanisms by which T cells are regulated are not thoroughly understood at this time, but tantalizing clues make this one of the most challenging aspects of biomedical research.

Histocompatibility Antigens

One question of great interest to immunologists concerns the genetic control of the immune response. Folklore has long held that certain diseases "run in the family," but it is only recently that researchers have begun to obtain a scientific understanding of why this might be so. Evidence has been building that, just as the color of one's eyes and hair can be inherited from one's parents, so might an individual's capacity to resist invasion from foreign substances. One of the defense mechanisms that appears to be under genetic control is the HLA system, historically named for Human Leukocyte Antigens, now known as histocompatibility locus antigens.

The immune system recognizes invading cells by the more than 6,000 marker antigens that are carried on cell surfaces. Production of these antigens is under the control of genes that are passed on from the previous generation. These antigens are like chemical fingerprints, each person's antigens are distinguishable from those of others. This identification system prevents an organism from mounting an attack against one of its own cells or organs.

Knowledge of this function and how it is regulated is useful when it is desirable to turn off the immune system, for example, in the prevention of rejection of an organ transplant when the tissue of the donated organ does not match the HLA type of the recipient. The HLA complex is also investigated when the question arises as to why the immune system doesn't recognize cancer as foreign. Perhaps the cancer masquerades as a normal cell by producing or donning the surface markers that cause the body to allow the cancer to go unrecognized.

Epidemiological studies support the view that certain HLA types are associated with an increased likelihood of developing certain diseases. For example, an individual born with the HLA marker known as B27 is 300 times more likely to develop ankylosing spondylitis (a form of rheumatism) than a person born without that particular marker. The presence of B27 alone is not enough to cause this disease to develop, many people born with B27 never do. Current theory holds that these individuals are particularly sensitive to a viral infection that, in turn, leads to rheumatism. Ongoing studies to match those diseases with their corresponding HLA types may help to identify high-risk individuals. In this way the severity of the illness may be lessened by early diagnosis and initiation of treatment, or averted altogether by appropriate interventions. In the case of B27, a vaccination against the guilty virus might prevent the onset of rheumatism.

Vaccines

Edward Jenner created the first vaccine in 1806, using live virus to confer immunity against smallpox. Cartoons drawn at that time indicated that people were afraid that the cow pox with which he inoculated his patients might transform them into cows. Since that time, of course, many dangerous diseases have been eradicated thanks to worldwide immunization campaigns.

Forty years ago, vaccine research virtually halted when the advent of miracle drugs such as sulfa compounds promised an end to bacterial disease. Efforts to produce vaccines to protect against infections such as meningitis, pneumonia, group B streptococcus and typhoid were abandoned until recently. Today, 30 percent of all drug prescriptions are for antibiotics. Indeed, today's tendency to rely on antibiotics to treat infections has actually impeded research on developing the means for infectious disease prevention. As more and more drug-resistant strains of bacteria arise, the vaccine route to prevention becomes more attractive. In addition, the most common infections are caused by viruses, which cannot be treated with antibiotics.

In the intervening years, a deeper understanding of the mechanisms underlying the immune response has enabled scientists to produce safer, more effective vaccines. They have found that it is not necessary to inject the intact microorganism, rather, specific subunits are enough to induce lymphocytes to recognize the invader and attack it. In order to minimize the adverse reactions that may follow inoculation with the actual disease-causing agent, vaccines were developed using only a portion of the foreign substance.

For example, polysaccharides, or carbohydrates taken from the cell capsules of bacteria can confer immunity to meningitis and pneumonia. Investigations are under way to try to develop a capsular polysaccharide vaccine against the strep B infections that affect thousands of neonates each year. Because babies cannot be immunized soon enough after birth to be resistant to infection, the new vaccine might be given to women of childbearing age. Consequently, during pregnancy, antibodies produced by the mother will cross the placenta and immunize the fetus.

Vaccine research has just come full circle. Breaking with the more recent tradition of using portions of pathogenic microorganisms as immunogens, scientists have found that the immune response can be enhanced when they vaccinate with a live virus that has been crippled so that it cannot cause pathologic symptoms.

Using this methodology, a new vaccine has just been developed against influenza, a disease which is responsible for annual epidemics that affect between 35 and 70 million Americans each flu season from late fall to early spring. Rather than the conventional injection delivery technique, this vaccine is administered via a nasal spray that may prove more acceptable to the public than current vaccines.

Also, researchers at NIH have prepared an especially long-sought vaccine against hepatitis. A particle containing the hepatitis B surface antigen was prepared in yeast cells using recombinant DNA techniques. This particle is immunogenic, and the procedure is convenient, inexpensive and safer than isolating live virus from the blood of carriers.

Monoclonal Antibodies

As described previously, antibodies are the body's first line of defense against infection. B cells were identified earlier as the lymphocytes responsible for making antibodies. Antibodies circulate in the bloodstream in

search of prey; the antigen. At first glance, all antibody molecules appear to be identical but closer inspection reveals differences that identify several tribes, known as idiotypes. This heterogeneity is the key to understanding how antibodies work, and how we can use them.

When the antibodies associated with its cell membrane encounter an antigen with a perfect fit, the B cell goes into a frenzy of division, splitting over and over, making several more B cells, all with antibodies of the same idiotype. If a foreign substance enters the bloodstream, several B cells respond, each to different parts of the invader, each producing an antibody of a particular idiotype.

In the past, antibodies were produced by injecting a substance into a research animal, collecting the serum and separating out the immunoglobulin or antibody-containing fraction. In that fraction of blood, there would be many antibodies against all the different immunogenic determinants that had been injected. The usefulness of antibodies obtained by this method is limited by the lack of antibody homogeneity so that the product might react with several different sites on that antigen molecule, or other compounds. Much effort was expended trying to inject the purest possible antigen, but there was always diversity in the antibody population due to the variety of responding idiotypes. The perfect solution to the problem of obtaining an antibody specific for only one antigenic determinant, would be to trigger a response in just one type of B cell.

One method for obtaining an antibody produced by a single B cell is to harvest just one antibody producing cell and then get that cell to reproduce itself over and over. This process is called cloning. However, activated B cells are notoriously difficult to maintain in continuous culture. Unless this tendency to die off over time is overcome, the B cells have limited value.

The hero in this B cell rescue is a kind of cancer cell, one capable of bestowing immortality. The type of cancer used is called a myeloma which is itself derived from B cells so that it retains the ability to sustain the functions that are necessary for B cell survival. When the activated B cell obtained from the spleen of an immunized mouse is fused with the myeloma cell, the product is a pure immortal antibody-producing cell, known as a hybridoma. The clones obtained from this single parent cell all manufacture the identical antibody.

The potential uses for monoclonal antibodies are extensive. The wide variety of tests that employed polyclonal antibodies in the past can be made infinitely more sensitive by switching to monoclonal antibodies. These include the procedures that quantify blood and urine concentrations of proteins such as hormones and enzymes, forming the basis for the diagnostic tests for pregnancy, some forms of cancer, etc.

Scientists all over the world are exploiting the specificity feature of monoclonal antibodies. Antibodies can be used to direct "guided missile systems;" that is, an antibody made against a particular cell type will find its way to that cell without affecting any others. By linking a drug or

radioactive tracer to the antibody, this technique may be used to home in on cancer cells or diseased organs that need treatment with agents that might harm other normal cells.

Conclusion

The immune system is extremely sophisticated in that it displays both enormous diversity and, at the same time, exquisite specificity. Different components work in harmony to protect against infection from a multitude of ubiquitous microorganisms and to distinguish foreign invaders from normal body parts. Recent advances in understanding the mechanisms of immunologic control have enabled scientists to manipulate the system to enhance its beneficial effects, or to escape its more irritating functions. In addition, the cells that produce weapons to fight infection can now be custom-designed and harnessed as the latest addition to the physician's arsenal of therapeutic agents.

Neurosciences

The human nervous system, awesome in its intricacy and capabilities, has for centuries remained an intractable biological enigma. The scope of problems inherent in studying the central nervous system (CNS) are staggering. Within the brain alone, there may be 100 billion nerve cells (neurons), perhaps as many as 1,000 billion. Each one of these cells is interconnected with other neurons. The number of these connections may well be in excess of 100 trillion. By comparison, the diminutive brain towers above the largest electronic computer in terms of complexity.

Morphologically, neurons exhibit an interwoven tree-like structure which has challenged and frustrated neurobiologists. Only with the fortuitous discovery of a staining technique by Camillo Golgi in 1875 and the dedicated work of the neuroanatomist Ramon y Cajal, did it become apparent that the neuron was indeed the basic building block of the CNS and that these cells were interconnected in a structured fashion.

Despite the difficulties, investigators have persisted in their efforts to understand not only the structure but the mechanisms of CNS function. Although there have been many advances during the 19th century, the last decade has witnessed a dramatic acceleration of accomplishments and opportunities within the neurosciences.

In spite of the impressive strides in understanding, the human nervous system still harbors countless mysteries. At this juncture, the neurosciences have defined the borders of a vast unexplored terrain. Some researchers have likened it to the discovery of the microbial world. Currently there exists the technology, expertise and core knowledge necessary to address age old questions surrounding the basis of thought, memory, learning, emotion and perception. The exploration of the mind has now begun.

The CNS is being aggressively studied from diverse perspectives, molecular through behavioral, invertebrates through man. Many of the current techniques and approaches used to further our understanding of the CNS have come from advances in other scientific disciplines, most notably biochemistry, immunology and genetics. CNS cellular functions are now being dissected at molecular levels. Today, scientists using highly sophisticated techniques can literally witness biochemical events as they occur within living nervous tissue during such mental states as sleep, anger, or hunger. As neurobiology has moved forward, the gap between the behavioral and biological sciences has narrowed.

A pivotal result of our new appreciation of the CNS is a greater understanding of many of the diseases which are either directly related or influenced by the nervous system. Never before have there been so many opportunities for sophisticated studies of neurological diseases which were heretofore treated in a totally empirical fashion.

The following discussion is intended to relay, in brief form, some of the major directions and areas of activity which are being pursued within the vast scope of the neurosciences.

The Neuron

Although there are other types of cells found in neural tissue, such as glial and Schwann cells, neurons constitute the fundamental operating element of the human nervous system. Only with a sound understanding of the neuron can one begin to comprehend CNS operation at higher organizational levels.

Although the basic morphology of the neuron has been known for some time, very little has been known about the neuron's functions and capabilities. Initially, neurons were viewed as rather simple transmitters of electrical impulses. New research tools and methods are now revealing a far more complex picture.

For many years, information regarding the electrical activity of neurons was collected using microelectrode probes. While such probes are valuable tools, they suffer a number of limitations. Advances in electronics have led to the creation of a technique known as "patch clamping." Now, minute changes in electrical activity within the neuronal membranes can be measured. This technique can also be used to modify the neuron's internal environment, thus an analysis can be performed on neuronal functions.

Each neuron may receive a variety of inputs, some of which may be either inhibitory or excitatory. The individual neuron then "evaluates" the incoming stimuli and executes a specific net action. It is now clear that signal transmission within the CNS is modulated countless times by individual neurons. Also, for some time it was believed that the chemical flow of information within the neuron proceeded in one direction only. Recently it has been demonstrated that dendrites can transmit as well as receive.

These are but some of the many notions concerning neuron form and function which are being refined and in some cases dramatically altered. This type of research is helping to construct a conceptual framework within which extremely complex mental processes can be explained.

Neurotransmitters

It has been shown that neurons are not in physical contact with one another but instead are separated by a small distance of space known as a synapse. In general, when a nerve cell is stimulated, it integrates the incoming information and releases chemicals at its axon (transmitting) terminal. These substances, neurotransmitters, quickly diffuse across the fluid filled synapse and bind to specific receptors in the postsynaptic membrane. These transmitters are not randomly found throughout the brain, but are localized in specific regions.

Over the years an ever greater number of discrete neurotransmitters have been discovered. Some well-known transmitters include acetylcholine, dopamine and serotonin. Although approximately thirty have thus far been defined, more

remain to be identified. Previously, it was believed that only one chemical message was transmitted at a given synapse. Now that it is realized that more than one neurotransmitter can operate at a given receiving terminal, the complexity of the brain takes on yet another dimension.

Investigations into the nature of brain peptides constitute one of the most active and exciting areas of neurobiology. Only within the last few years has it become apparent that such hormones can act as neurotransmitters, neuromodulators or co-transmitters and that they are involved in regulating homeostatic systems throughout the body. They are further involved in the control of behavioral systems linked to learning, memory, stress and pleasure. There are clear implications that our understanding of both normal and morbid behavior will progress greatly as research advances reveal the mode of action and the functional role of these peptides.

An area of particular interest concerns the perception of pain. For centuries the analgesic effects of opium have been known. Equally known are its side effects, namely, increasing tolerance, dependence and eventual addiction. It was discovered in the mid-70's that a class of naturally occurring neuropeptides, the enkephalins and endorphins, bore a striking chemical similarity to morphine in their mechanism of action. This discovery followed the finding that specific receptors in the brain strongly bind opiate drugs. This line of research has important implications for the management of pain and control of undesirable side effects related to existing compounds. By gaining an understanding of the biochemical basis of sensory perception, there is a real opportunity to design drugs that avoid pathophysiological effects while retaining their therapeutic qualities.

As we learn more about each specific neurotransmitter, its role and relationships with other neural chemicals and its effects on the receptive neuron, our picture of the mind's operation sharpens. Such a finding moves us closer towards understanding the very basis of complex mental activities.

Neural Regeneration

Unlike other tissues, once a brain cell is destroyed another cell will not grow, divide and replace it. This makes the CNS of higher animals particularly vulnerable to injury. This is not true for all neural tissue. Nerves outside of the CNS, such as those severed in the hand or foot will regenerate. It is clear that injured neurons have the ability to grow back, yet within the CNS some unknown factor(s) prevent this from happening. The challenge is further complicated in that not only must the nerves be promoted to grow, but regenerating nerve fibers must align themselves with specific targets. A number of experimental approaches are now focused on the problem of neural regeneration.

A variety of animal models are being studied in which nerve tissue regeneration can be observed in an effort to elucidate the mechanisms of regeneration. There is some evidence to suggest that an independent mechanism within the neuron determines the extent of nerve process regeneration.

Other research has suggested that specific tissue factors may promote the growth of nerve tissue. Some investigators are attempting to detect the signals which direct neurons to restore normal cell configuration and function. Another line of work involves developing a greater understanding of the cells which provide the supporting "ground substance" upon which sprouting nerve fibers extend themselves. Such cells, namely Schwann cells, glia and fibroblasts may all play an important role in the regenerative process. Yet another effort is based upon efforts to transplant healthy neural tissue into damaged areas of the brain.

Mechanisms of Behavior

The number of methods available to study the brain during different behavioral states has dramatically expanded. The operation of the mind is being examined both at the level of a single neuron and entire regions of the brain. These advances are due to techniques using radioactive nuclides which measure the level of metabolic activity taking place at different regions of the brain. Highly specific monoclonal antibodies are employed in classifying neurons into known types and describing their distribution. Imaging techniques such as positron emission tomography (PET) are revealing which sections of the brain are active during different behavioral states.

A recent example of such work involves the discovery of what appears to be appetite receptors in the brain. This finding may enable the development of drugs which could control abnormal appetite without the undesirable side effects of drugs that are currently used. Such work could lead to a unified theory of how appetite is regulated.

Alzheimer's disease, which affects a significant number of the elderly, is characterized by loss of memory, irritability, disorientation and an inability to function within one's normal environment. It was once believed that this disorder was part of the normal aging process; however, this is no longer the case. For some time, neurologists could characterize the disease by the presence of neuritic plaques and tangles. Researchers were disheartened due to the non-specific distribution of these changes throughout the cortex. Recent work now suggests that one region of the brain, the nucleus basalis of Meynert, may hold the key in explaining the deterioration and death of cells throughout the brain. This new evidence is the result of a series of investigations, employing many techniques, which defined the metabolic function and viability of neurons within specific regions of the brain. Currently, it appears there is a strong correlation between the loss of cells in the nucleus basalis, the number of neuritic plaques, and the severity of the disease. Researchers are quick to point out that there may be other factors involved; yet, for the first time, neurologists can focus their attention on a specific population of cells that play a key role in the progression of the disease. These new insights in neurophysiology offer hopes of developing a fuller understanding of the disease, leading to prophylaxis and treatment.

Instrumentation

Early investigative research involved one key instrument, the human mind. Observation and analysis comprised the fundamental approach to questions surrounding the processes of life and disease.

Surgical and dissection instruments may have been the first tools employed in attempts to understand life. Beyond the work of early anatomists, for many centuries inquests in biology proceeded without the necessity of instruments. The chief need for precision devices occurred in the fields of astronomy and navigation. It was within these areas that most early advances in instrumentation took place.

By the 16th century significant improvements had been made in the field of optics. It was discovered that by mounting a number of lenses together in a tube one could create an instrument of considerable magnifying power. Such an instrument is called a Galilean telescope when viewed from one end and a Galilean microscope when viewed from the other. Although primarily known for his work in astronomy, Galileo is credited with making the first biological observations using such a microscope. Others improved upon the design, and a series of early microscopists made discoveries which had a profound influence on biology.

With the advent of the microscope it was possible to develop a general theory concerning the basic organizational structure of plants and animals. Although it wasn't until the mid-1800's that the cell theory was postulated, the importance of instrumentation in the biological sciences was firmly established. It became clear that the test of new ideas and creative theories required more than imagination; the extension and quantification of human senses and capabilities was necessary.

As science moved into the 20th century, the interrelationships between the progress of knowledge and advances in instrumentation became ever closer. The devices which are used by today's researchers are intimately interwoven into every aspect of biomedical research and clinical practice; thus, the topic of instrumentation is one of exceptional breadth and complexity.

The advancement of knowledge often hinges on technological advances which allow new forms of experimentation. Likewise, the state of research instrumentation is often driven by scientific opportunities and need. In some cases technology leaps ahead of scientific thought and may not be effectively employed for some period of time. At other times, new theories languish until a means for testing their validity is available.

Instruments have now reached unprecedented levels of precision and sophistication. Machines have extended human senses to a point where normal and disease processes can be examined at their most basic levels. The following sections are intended to highlight some of the areas in which such advances in instrumentation are opening new and exciting opportunities for biomedical research.

Imaging Devices

In 1895, W. K. Roentgen discovered what were later called x-rays, and that this form of energy could pass through solid objects and fix images on photographic plates. Within a short span of time, x-rays were employed in both research and the practice of medicine.

Over the years there have been numerous improvements in the use of X-ray technology. Also, within the last ten years, the ability to image biological structures has dramatically improved through the introduction of other techniques which have features surpassing the capabilities of X-ray devices. In a large part, these advances stem from the marriage between advances in physics and computer science. A number of these new technologies will be briefly described.

Nuclear Magnetic Resonance (NMR). NMR is based on the principle that the atomic nuclei of many elements, some of which are present in human tissue, are akin to tiny spinning magnets. When these "magnets" are placed in a strong magnetic field, their nuclei will line up in the direction of the field. A second magnetic field is turned on which is at a right angle to the first. When this second field is turned off, the nuclei will resume their original attitude, and, in the process, release detectable signals that a computer can process and display as an image.

NMR is an extremely effective tool for examining soft biological tissues. Unlike X-rays, NMR does not pose a risk in terms of ionizing irradiation. In addition to imaging the morphology of tissue, it can reveal a great deal about the underlying biochemical events which take place within living organisms.

The development and applications of NMR in medicine and research is just beginning. Some current applications of NMR include:

- Revealing tumors earlier and more effectively than conventional techniques;
- Measuring tissue metabolic alterations and accessing the effects of drugs and other therapies;
- Measuring the viability of organs before they are used for transplantation surgery; and
- Detecting fatty deposits in arteries before they are evident by other means.

Researchers are confident that NMR will play an ever increasing role in both diagnostic and experimental medicine.

Ultrasound. Frequencies in the order of millions of hertz are far above the range of human hearing. As early as 1930 it was proposed that such "sound" could be used to non-invasively probe the human body employing the same principle as that involved in radar and sonar. The first attempt to use ultrasound on the human body came in 1943 when Karl T. Dussik tried to map the anatomy of

the brain. The attempt failed. However, research continued and in 1957 a Japanese researcher, Shigeo Satomura, reported the first successful measurement of moving organs within the body using pulsed ultrasonic signal echoes.

Ultrasound technology has advanced to a state where it is now possible to construct 2-dimensional images of the internal structure of the body. Ultrasound imaging has advantages over x-rays and some other imaging approaches in that it is safe and relatively inexpensive.

Ultrasound has a broad range of application, particularly in cardiology and obstetrics. Some current applications in obstetrics include:

- Estimation of gestational age for patients with uncertain clinical dates, or verification of dates for patients who are to undergo scheduled elective repeat cesarean delivery, indicated induction of labor, or other elective termination of pregnancy. Ultrasonographic confirmation of dating permits proper timing of cesarean delivery or labor induction to avoid premature delivery.
- Evaluation of fetal growth (e.g., when the patient has an identified etiology for uteroplacental insufficiency, such as severe pre-eclampsia, chronic hypertension, chronic renal disease, severe diabetes mellitus, or for other medical complications of pregnancy where fetal malnutrition, i.e., IUGR or macrosomia, is suspected). Following fetal growth permits assessment of the impact of a complicating condition on the fetus and guides pregnancy management.
- Identification of the source of vaginal bleeding of undetermined etiology in pregnancy, and determination of the status of the fetus.
- Determination of fetal presentation when the presenting part cannot be adequately determined in labor or the fetal presentation is variable in late pregnancy. Accurate knowledge of presentation guides management of delivery.
- Suspected multiple gestation based upon detection of more than one fetal heartbeat pattern, or fundal height larger than expected for dates, and/or prior use of fertility drugs. Pregnancy management may be altered in multiple gestation.
- Adjunct to amniocentesis. Ultrasound permits guidance of the needle to avoid the placenta and fetus, to increase the chance of obtaining amniotic fluid, and to decrease the chance of fetal loss.
- Significant uterine size/clinical dates discrepancy. Ultrasound permits accurate dating and detection of such conditions as oligohydramnios and polyhydramnios, as well as multiple gestation, IUGR, and anomalies.

Another major clinical use of ultrasound today is in the so-called M-mode echocardiography which permits display of movement of cardiac structures along a single axis. This method makes possible the diagnosis of cardiac enlargement, valve abnormalities, and fluid collections about the heart.

Positron-Emission Tomography (PET). Although the morphology of biological structures provides insight into biological processes, an appreciation of the underlying biochemical events is often essential in understanding the nature of a given disease. In most cases, early biochemical events precede biological changes that can be detected by x-rays, including CAT scans. Positron-emission tomography is a method of examining, with a high degree of precision, biochemical events that take place within the body.

PET involves labeling a biologically active compound with a radioactive isotope. The isotope emits a positron upon decay, and it immediately interacts with an electron, whereupon two gamma rays are generated, flying off in opposite directions. A ring of sensitive detectors collects information on the gamma rays as they leave the body of the subject. A computer analyzes the information and constructs a spatial distribution of the radioactive material within the subject, thus identifying the location of specific metabolic activity within the body.

PET can be used in a wide variety of diagnostic and research settings. It is an exciting technique in that it provides a picture of biochemical and metabolic processes. Some of the applications of PET include:

- examining the extent of myocardial infarctions and predicting the relative success of various surgical procedures;
- evaluating the extent of blockage suffered by stroke patients;
- mapping regions of mental activity within the brain identifying malfunctions associated with such disorders as epilepsy, Parkinson's disease, head injury, brain tumors, and dementia; and
- detecting other types of malignancies.

Computers

Automatic data processing devices continue to play an ever increasing role in biomedical research. In many ways their presence is so ubiquitous and dynamic that almost any set of examples will fall far short of conveying an adequate appreciation of their current and potential applications.

- Computers are used to enhance the imaging of microscopes. Digital imaging-processing techniques perform complex contrast enhancement, edge detection, background subtraction, pseudocolor enhancement and tracking functions. Similar techniques can also improve the image quality of X-ray photographs.
- Computer programs are now being developed and utilized which mimic the complex process of disease diagnosis. Such programs attempt to capture and structure the body of knowledge which underlies the heuristic decision-making process employed by physicians during diagnosis. In some cases such systems have a greater than 90 percent success rate (of diagnosis) even when confronted with difficult cases. These programs are not intended to replace doctors but to augment their skill,

providing expert advice in specialized areas. Primary care physicians and physician's assistants working in the field or in remote areas may find such programs of great value.

- Computers serve as readily accessible data bases which are generally designed to serve specific populations of users, such as clinical oncologists or organic chemists. Many modern systems can provide users with a range of information going far beyond simple citations. In one case, a system has been designed which allows investigators to compare the nucleic acid sequence of proteins produced in their laboratories with the sequences of other known proteins kept in a data bank. Such information can provide important clues regarding the function of a given molecule.

Lasers

Lasers, born in the physics laboratory, have found a number of useful applications in the area of biomedicine. Their use is sometimes obscured by the fact that they are incorporated into the internal working of some other device, such as an automatic cell sorter. In other cases the laser is used in a more direct fashion. The following sections are but a few examples of how lasers are being used in biomedicine.

The Laser Microbeam. The laser microbeam is a device that produces a tight beam of amplified light ten billions of a meter in diameter. A microbeam is created by projecting laser light through a light microscope. The resulting beam can then be used as a microscopic probe which can pinpoint with extreme accuracy tiny cellular structures. The beam can destroy specific molecular constituents of selected organelles within a cell, thus revealing information about the function and interrelation of cellular components. The beam is so delicate that it can literally dissect chromosomes, allowing researchers to investigate the mechanisms of heredity.

Photoradiation Therapy. Research is being conducted in which laser light is used to stimulate tumor-binding dyes that are able to destroy some types of cancer cells that are resistant to other forms of therapy. This technique involves injecting the tumor host with a nontoxic, photochemically active agent. After a short period of time, little of the agent remains in normal tissue but high concentrations remain in tumor tissue. Finally, the patient is exposed to red laser light, activating the dye which is then toxic to cancerous cells.

Laser Surgery. Lasers have been found to have increasing applicability in surgical procedures. The energy from different lasers, argon vs. krypton, are absorbed differentially by different sorts of tissues. In one case, researchers are using an argon laser to coagulate red blood cells around a severed nerve. The white nerve fiber largely reflects the light, while the red blood cells absorb it. The laser has already been used extensively in ocular surgery. For example, laser treatment can prevent age related breakdown of the macula (the point of clearest vision in the retina) and is effective in treating diabetic retinopathy.

SECTION II--THE NIH PLANNING FUNCTION

DESCRIPTION OF THE PLANNING FUNCTION IN THE OFFICE OF THE DIRECTOR, NIH

Introduction

The planning function in the Office of the Director (OD), NIH, encompasses a set of activities designed to increase the overall effectiveness of the agency in developing, under a wide range of circumstances, knowledge in the biomedical and behavioral sciences which will lead to safe and effective interventions in man. The mission of the NIH, its organizational structure, and the knowledge development process which characterizes the course of research all provide the context within which these activities are initiated and pursued.

Mission

The mission of the National Institutes of Health is to improve the health of the Nation by increasing the understanding of processes underlying human health, disability, and disease; advancing knowledge concerning the health effects of interactions between man and the environment; and developing and improving methods of preventing, detecting, diagnosing, and treating disease.

NIH accomplishes this mission through--

- Support of biomedical research in universities, hospitals, and research institutions in this country and abroad;
- Conduct of biomedical research in its own laboratories and clinics;
- Support of training for promising young researchers;
- Development and maintenance of research resources;
- Identification of research advances that have significant potential for clinical application, and the facilitation of the transfer of such advances to the health care system; and
- Promotion of effective ways to communicate biomedical information to scientists, health practitioners, and the public.

Biomedical research involves a continuing search for knowledge. Basic biomedical research is, by its nature, an unpredictable undertaking; there is no way of forecasting which problems will yield easily and quickly, nor when solutions will be found. This has always been characteristic of the course of biomedical research and will continue to be.

Nevertheless, we are coming closer than ever before to understanding the basic mechanisms of the living processes in cells and tissues, and there is a

high degree of confidence that the underlying mechanisms of disease are becoming approachable because of these insights. This view is rapidly replacing the view held by many that the study of disease is quite a separate endeavor from basic research. The evidence is also growing that human diseases are not the completely separate and apparently unrelated entities that they were once believed to be, and as we continue to identify and sort out the participating factors in the causation of disease, the knowledge gained will advance our understanding on multiple fronts. .

In the more applied areas, the emphasis placed upon the conduct of clinical trials in the past decade has played a role in altering established medical practice in the treatment of numerous health problems, while at the same time raising challenging questions. A recent addition to the fabric of health research is the structured effort to assess the broad clinical significance of new applications through consensus building and the communication of results to those who can use them. This activity has called our attention to how much we know in certain areas, as well as to our shortfall of knowledge, all of which moves our research effort closer to more rational intervention.

The health mission of the NIH, and the manner in which that mission is carried out through the conduct and support of biomedical research, significantly condition the OD planning function and the principal activities through which the function is implemented.

Organizational Overview

To carry out its mission, the NIH is organized into an Office of the Director, three research bureaus, eight research institutes, one research division, three service divisions, and the National Library of Medicine. The organization also includes the Clinical Center--a combined research hospital and laboratory complex--and Fogarty International Center, which fosters international biomedical research collaboration. All of the NIH Institutes, the Division of Research Resources, the Fogarty Center, and the National Library of Medicine have individual Congressional appropriations. Funding for the service divisions and the Clinical Center comes from the Management Fund (built into the appropriation for each BID) and the service and supply fund (a fee for service arrangement). In total, the NIH receives 16 separate appropriations each year.

The three bureaus and four of the institutes focus on specific diseases: cancer; heart, lung, and blood diseases; arthritis, diabetes, and digestive and kidney diseases; neurological and communicative diseases and stroke; vision disorders; allergy and infectious diseases; and dental diseases. At three institutes there is a more general health-related focus--on child health and human development; aging; and environmental health. The focus of the National Institute of General Medical Sciences is on increasing knowledge in the fundamental life sciences. The Division of Research Resources has responsibility for strengthening and enhancing the institutional environment through support of a wide variety of essential research resources used by investigators.

The typical NIH Institute includes both an extramural and an intramural program component. The extramural programs are responsible for roughly 80 percent of NIH's resources in the form of research grants or contracts. Through these programs, NIH makes approximately 20,000 awards of various kinds to more than 1,200 institutions in every state of the Union and to a number of foreign countries. Extramural awards are based on a two-tiered peer review assessment--one for technical merit and one for program relevance. Nearly all of the NIH Institutes also have an intramural component of laboratory and clinical research programs. Over 2,500 research projects are in progress at all times, making NIH the largest center for biomedical and behavioral research in the world. The intramural program, while smaller in dollars (roughly 13 percent of the annual NIH budget), requires somewhat more than half of total personnel resources for direct laboratory and clinical research on the Institute's assigned problems. Boards of Scientific Counselors are responsible for assessing the quality and direction of the intramural program.

In the Office of the Director (OD), in addition to the Director, there is a Deputy Director, a Deputy Director for Intramural Research, and a Deputy Director for Extramural Research and Training. The OD has major staff offices including Administration, Extramural Research and Training, Research Services, Program Planning and Evaluation, Communications, Medical Applications for Research, International Affairs, Clinical Care, and Intramural Affairs. There are special assistants to the Director for clinical trials and epidemiology, research training, and prevention.

Statutory Authorities

The main legislative authorities to support the NIH research mission are contained in Titles III and IV of the Public Health Service Act. Since that Act was codified in 1944, most NIH programs have drawn on the broad research authorities in Section 301, which operate without time or dollar limits. This broad mandate authorizes collection and dissemination of scientific information, awarding of grants and contracts for research, general research support, hiring of consultants from the United States or abroad, admission and treatment of patients at the Clinical Center, and the general conduct of research, including such specific areas as testing for harmful substances, human nutrition, and biological effects of low-level ionizing radiation. Approximately 60 percent of the total NIH budget draws on the legislative authorities of the Public Health Service Act. As principal exceptions, specific program authorizations with time and dollar limits have been enacted for a number of other programs.

The Congress has influenced both program and policy at NIH through the authorization-appropriation process, including both the introduction and the passage of specific legislation and Report language expressing the wishes and intent of the Congress, and through the oversight process.

Public laws focusing on NIH activities have ranged from the general, such as the National Sickle Cell Anemia Control Act (P.L. 92-294) of 1972, which established a national program focused on this disease, to the very specific, such as the Orphan Drug Act (P.L. 97-414) of 1981, which had as one of its provisions a requirement that the National Heart, Lung, and Blood Institute

fund ten Sickle Cell Centers. The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423) is a further example. This act expanded on the broad mandates for the National Heart Institute's research program and also reflected an intervention by the Congress into program management through the requirement that at least 15 percent of the Institute's funds be allocated for programs in lung diseases and blood diseases and blood resources. Authorizing legislation pending in the 98th Congress also reflects this range from general interest in health issues to detailed specification of program priorities. For example, the NIH reauthorization bill recently passed by the House requires a number of very specific program and policy activities, but the bill also contains provisions reflecting the interest of the authorizing committee in some overall aspects of biomedical research and the operation of NIH. The enactment of this bill would likely have enormous impact on the NIH planning process, since it would require major program changes.

The appropriations process also provides an opportunity for expression of congressional concern and for influence of Congress on NIH programs and on the process of planning those programs. The most obvious example of this is the use of the "line-item" appropriations or "earmarks," whereby the appropriations bill provides funds for a specific activity. In general, the Congress has used this device to a minimum, choosing instead the more subtle approach of directing the allocation of resources through language in the Report accompanying the bill. Although Report language, does not, de facto, have the force of law, it is taken most seriously by NIH program administrators, who attempt, as much as possible, to follow it. Two recent examples are Senate Appropriations Report instructions "the Committee intends that a portion of the increase provided for the Institute be allocated to" research in multiple sclerosis and "the Committee believes it important that" funding for the Guam Neurological Disease and Stroke Center continue. In the event that these programs were planned either for discontinuation or substantial reduction, the relevant Institute is now constrained at the minimum to reconsider its plan or, perhaps, to revise it altogether.

Finally, Congress influences NIH programs and the planning process, without enacting legislation, through the oversight process. A recent example of this is congressional interest in AIDS research. Although the PHS had certainly recognized the problem and had taken steps to increase both research and surveillance activities, the Congress (by its mission and mandate reflecting the needs and concerns of the public) expressed in a number of ways the view that much more attention ought to be paid to this problem. The outcomes of that congressional interest were more resources allocated to this area, both through additional appropriations and through administrative actions, and redirection or refocusing of relevant program activities. The response of the Administration and, in particular, of NIH, in this regard ought not to be construed negatively; i.e., that NIH is not responsive to public need unless pressured by the Congress. On the contrary, such a response demonstrates that NIH has the flexibility necessary to respond to newly identified concerns and is willing to respond. Although these kinds of specific programmatic responses are undoubtedly somewhat disruptive of the total planning agenda, that they are not disastrous reflects an appropriate flexibility of the process.

In summary, congressional influence over NIH and, by extrapolation, over the planning process takes a number of forms not always visible through enacted legislation. Furthermore, congressional interest in NIH programs appears not to have waned over time and can be expected to continue. In fact, that interest has become increasingly specific and, as such, will probably have increasing influence on the NIH planning process.

Office of the Director Planning Function

Given the mission of the NIH, the dynamics of the knowledge development process, and the organizational structure of the Agency, the scope of the OD responsibilities can be summed up as providing leadership, direction and guidance to the national biomedical research effort. Maintaining the health and vigor of the enterprise as a whole underpins all OD responsibilities. The development of national biomedical research policy, the setting of national priorities, the allocation of resources, the establishment of research strategies, the coordination of cross-cutting research initiatives, and the management of the effort are all essential responsibilities incorporated into the OD's leadership role. All major staff offices in the OD participate in the execution of these responsibilities although their role and level of involvement varies. The BIDs, the Director's Advisory Committee, outside professional groups and health organizations, congressional committees and Executive Branch offices all interact with the OD and influence the execution of these responsibilities.

The OD planning function provides a structure through which many of the decisions required as a consequence of the OD responsibilities can be considered in a systematic fashion by bringing together appropriate major staff offices, groups and interests in a collective effort designed to achieve consensus on policy direction, priority-setting, resource allocation, and research strategy issues.

Overview of Planning Activities/Organizational Locus

Although each major staff office participates in the OD planning activities, the principal organizational locus for these responsibilities resides in the Office of Program Planning and Evaluation (OPPE). In OPPE, the planning activities are carried out in the immediate office of the Associate Director for Program Planning and Evaluation and in the Program Planning Branch; six professional staff direct and manage these activities. All functional areas represented in OPPE (evaluation, legislative analysis, and program analysis) contribute directly and on a consistent, structured basis to the planning activities. These relationships are essential to assuring the consideration of evaluation study results in all planning activities and the provision of a sound basis for action that may be sought through legislative channels. The planning activities also relate closely to and are coordinated with each BID planning function, the OD budget formulation and execution function, and the OD intramural and extramural management functions. The outcome of many planning activities ultimately are implemented through the budget process, affect BID decisionmaking and are incorporated into the management structure; consequently, linkages amongst these functions becomes crucial to assimilating planning activities across organizational structures.

The major activities which comprise the OD planning function include:

- the development and analysis of policy and the conduct of major issue analyses and studies,
- the identification of and planning for cross-cutting activities,
- the management of the Agency's central planning process,
- the management of the Director's Advisory Committee, and
- the development of proposals responsive to both HHS and PHS planning requirements.

Policy Development and Analysis

Policy development and analysis is an ongoing activity associated with the planning function, involving consideration and modification of existing policy approaches as well as responding to new, emerging issues. Most activity tends to be of the former type. Rather than entirely new issues being raised each year, recurring issues and concerns tend to take on new or changing perspectives or gather additional impetus over time. Policy development and analysis at the OD level addresses issues and concerns which tend to cut across organizational structures and individual program boundaries and are characterized as having broad significance within the Agency, as well as to the biomedical research community. The following characteristics typify the policy development and analysis activity:

- assignment of the issue/concern to a lead OD office. Usually this involves the Office of Program Planning and Evaluation, and, subsequently, the Program Planning Branch, but not always. The nature of the issue and OD staff expertise are considered in principal staffing responsibility. To the extent that the particular policy concern does not center on a single major aspect of a defined activity or functional area, the OPPE usually serves as the focal point within the OD for policy development. When OPPE is not assigned a lead responsibility, it usually plays a contributory role in the eventual formulation of specific policies.
- development of an analytic process which strikes a reasonable balance between "top-down" and "bottom-up" approaches. The analytic process can take many forms but usually involves guidance from the Director, NIH, and the establishment of a mechanism to assure the advice and direct participation of the BIDs and appropriate OD staff. Planning, legislative and evaluation staff are broadly represented to provide the necessary interaction among these functions, and to assure adequate follow-through.
- broad review of proposed policy position or modification. An integral part of the decision-making process involves an extensive review and assessment of proposals by major OD staff offices, BID staff, representatives from the biomedical research community, and in many cases

higher levels within the Administration. Parties affected have an opportunity to weigh the impact of particular proposals and suggest adjustments. This approach is designed to achieve broad consensus prior to final Agency decision-making. This review encompasses assessments of the impact of the particular proposal on resource requirements, Agency legislative authorities, operating procedures, as well as Agency priorities and strategies.

Cross-Cutting Activities

The knowledge development process that characterizes the course of biomedical research does not always follow organizational lines or program boundaries. This is both a natural and essential phenomenon of the conduct of research, one to be encouraged in as many ways as possible across a broad range of scientific disciplines and areas of research, program areas, and health problems. One of the major responsibilities of the OD planning function is to actively identify and plan for those areas of research which extend beyond the interests of any single BID and would profit from a more organized effort. Approaches in implementing this responsibility will vary depending on the area of research and the organizations involved. Some of the mechanisms by which cross-cutting activities are conducted and which reflect the OD planning role include:

- Area of research--A major planning effort led by OPPE several years ago resulted in the identification of and planning for a number of research initiatives that cut across both BID and agency lines. One such initiative was the accelerated development of new vaccines. The purpose of this program is to develop a clearly identified, widely recognized, and well coordinated approach to the further conquest of vaccine preventable diseases. The new knowledge and technologies which have been emerging from basic research in recombinant DNA and hybridoma technologies and in the better understanding of the workings of the immune system now provide opportunities to solve problems that have been insoluble with earlier technology and knowledge. Such new knowledge will permit radically different approaches to some of the current problems of immunization. The goal of the program is to expedite the availability of needed vaccines through the selection of a few candidate vaccines for intense and expanded effort so as to bring these vaccines into use several years earlier than might otherwise have been the case. This program contains projects directed at all necessary aspects of vaccine development from some fundamental studies on the etiologic agents through identification of the immunogenic antigens to developmental studies on vaccine production. An expanded initiative on development and subsequent use of new and improved vaccines supports the DHHS policy to emphasize the prevention of disease.
- Health initiative--In October 1981, the Special Assistant to the Director for Research Related to Disease Prevention was appointed by the Director to assist in implementing the NIH Disease Prevention Initiative. In January 1982, the trans-NIH Committee for Research Related to Disease Prevention and Health Promotion was established. In addition to providing the primary linkage between the Office of the

Director, NIH, and the BIDs, the Committee is also responsible for cataloging, analyzing, coordinating, and identifying research opportunities in disease prevention and health promotion. NIH Prevention Coordinating Committee members recently performed an extensive examination of the scientific review process for prevention-related studies pertinent to their respective institutes. The FY 1983 accounting of NIH prevention activities utilizes the newly proposed Departmental definition that is backed up by the proposed Guidelines for Categorizing NIH Research Related to Disease Prevention. It is anticipated that both the NIH guidelines and the Departmental definition will be slightly modified over the next two months.

- New function--In 1978, on the basis of position papers developed in OPPE, the NIH decided to extend its mission and undertake in selected circumstances to assess the results of clinical trials and create state-of-the-art reports on the drug, device, procedure, or medical practice under consideration. This activity is known as technology assessment and consists of synthesizing complex scientific information in such a way that the reports are useful for decision-making by practitioners or policy makers. Technology assessment, by either traditional mechanisms such as review articles by opinion leaders, or formal statements from professional committees or government agencies, is increasingly recognized as an essential step in the transfer of new research knowledge to medical practice. The focal point for technology assessment and transfer at the NIH is the Office of Medical Applications of Research (OMAR) in the Director's office. The NIH also sponsors a number of workshops, symposia, and conferences intended to assess the medical value of new therapies and the relevance of new knowledge to clinical practice. The most well known of these are the Consensus Development Conferences, which are sponsored jointly by one or more institutes and OMAR. These conferences bring together biomedical researchers, practicing health professionals, and representatives of the public in a scientific meeting to examine a specific health care technology.
- Health problems--In such areas as diabetes, arthritis, nutrition, and chronic renal disease, the Director, NIH, has established coordinating committees to oversee activities. Some of the committees operate under a lead institute concept (such as diabetes), while others are staffed and operated at the OD level (such as nutrition). The committees function to: (1) provide a forum for the exchange of information and the discussion of ideas and views; (2) strengthen and improve the NIH information systems for reporting on research and related activities in these areas of special interest; (3) facilitate discussion of specific areas of mutual interest and need; (4) identify areas of potentially wasteful duplication of effort; and (5) provide a focus and central point of contact for the NIH in dealings with other Federal agencies and outside organizations. These committees also serve to: (1) promote the development of joint program announcements and requests for applications (RFAs) to alert the scientific community to specific goals, research needs, special funding plans, and opportunities in

specific areas of research; and (2) facilitate the joint sponsorship of workshops, conferences, and symposia designed to identify areas of research need and to stimulate research in areas of highest priority.

- Program area--The NTP was established by the Secretary, DHHS, in 1978, for the purpose of strengthening the Department's activities related to the testing of chemicals of public health concern and the development and validation of new and better test methods. The program is comprised of the relevant activities of the Food and Drug Administration (FDA), the Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH), the National Cancer Institute (NCI), and the National Institute of Environmental Health Sciences (NIEHS). Specially dedicated resources of these agencies support the program activities of the NTP. To manage the resources and lead the program, the Director, NIEHS, serves as Program Director, and is responsible to the Assistant Secretary for Health, DHHS. To ensure the appropriate interaction of research and regulatory interests, the principal health regulatory agencies are invited to participate in the NTP. These "participating agencies" include the Occupational Safety and Health Administration (OSHA), Department of Labor; the Consumer Product Safety Commission (CPSC); and the Environmental Protection Agency (EPA).
- Public health emergency--One notable recent example of such an effort is the collaborative program mounted to combat an outbreak of a condition, referred to as acquired immune deficiency syndrome (AIDS), in which previously healthy persons acquire a malfunction of the immune system leading to the development of neoplasms such as Kaposi's sarcoma and the occurrence of rampant opportunistic infections. The NIH, in collaboration with the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA) is conducting and supporting studies to identify the agent or agents responsible for AIDS, to understand the mode of transmission and the factors that contribute to risk, and to develop and evaluate tests and procedures for identifying and excluding blood and blood products from donors at increased risk for AIDS. Several working groups have been established within the OD, NIH to facilitate discussion and collaboration in this area. One working group is designed to assure the dissemination of current information to all key participants and the other working group, to identify research leads and to develop strategies to guide further action in this area. Special workshops and symposia have been convened, and the BIDs are providing substantial extramural support for research on this problem as well as mounting intramural research investigations.

These examples of different types of cooperative arrangements serve to convey the range of possibilities that exist for collaboration and the extent of the initiative taken by the OD in carrying out this critical planning activity. New mechanisms and organizational arrangements for achieving effective collaboration will continue to be developed and tested, and the appropriate roles of the various partners in these joint ventures will undoubtedly evolve as experience is gained through further participation in such collaborative activities. The Director, NIH, has the managerial flexibility necessary

to initiate such collaborative arrangements and through both the central planning process and the OD policy development activities is in a unique position to identify the need for such arrangements and to monitor their progress.

NIH Central Planning Process

Over the past seven years, the NIH has strengthened and improved its central planning process in order to ensure that the most promising scientific opportunities are identified and pursued, that limited resources are effectively used, and that NIH programs are responsive to legislative mandates and to broad health objectives established by the Assistant Secretary for Health and the Department. Highlights of some of the factors considered and processes followed in planning for research opportunities and in establishing priorities are summarized below.

- Planning Agenda Development--In October of each year, the Agency's formal planning process is initiated by OPPE through the development of an agenda which outlines the NIH's overall directions and research strategies, priorities designed to maintain a vigorous national effort and to guide the subsequent allocation of resources, and policy issues requiring examination during the year. The planning agenda serves as the principal source planning document for discussion of the Agency's plans with the Assistant Secretary for Health, which usually occurs in November of each year. This effort results in the initial establishment of NIH approaches and priorities for the planning year, provides the context for subsequent program development and resource allocation decisions, generates a set of agreements with the PHS designed to be responsive to and supportive of broader health objectives and priorities, and results in the identification of major issues requiring further consideration.
- Planning Sessions--The purpose of these sessions, held in December and January of each year with each BID, is to brief the Director, NIH, for the Appropriation Hearings and to provide initial information and justification needed by the Director to review scientific opportunities of high priority proposed for the planning year. These sessions provide a forum for interaction and decision-making between the Director, NIH, the NIH Institute Directors and their respective senior staffs, result in mutually useful briefing in preparation for the Congressional hearings, serve to initiate action leading to the resolution of program issues, stimulates the development of initial research strategies for the planning year, and facilitates the identification of high priority areas of scientific opportunity. In addition to senior BID staff, all major OD staff offices participate in these sessions which are directed and managed by OPPE.
- Budget Review Sessions--The purpose of these sessions, usually held in early spring each year between the Director, NIH, and the BID Directors, is to refine the NIH research and budget strategy under varying assumptions and constraints, firm up Agency priorities, and review the impact of policy decisions in this context. These sessions result in guidance for refining plans for significant program changes at the BID

level and final decision-making on high priority scientific opportunities to be pursued during the planning year, as well as initial resource allocations to each BID. These sessions also form the basis for the development of planning and budget proposals which are subsequently transmitted to the Administration in the NIH Research Plan and the Preliminary Budget Submission. Program plans and resource allocations developed from these sessions are formally discussed with the Assistant Secretary for Health prior to transmission through organizational review channels.

- NIH Research Plan--This document is based upon and reflects the outcome of all major events encompassed in the central planning process. The major program changes and scientific opportunities to be pursued which are presented in the plan are an outgrowth of priority and resource allocation decisions developed through the central planning process. The plan is published without budget estimates to conform with Administration requirements; however, when transmitted through formal review channels these decisions are also displayed. The NIH Research Plan is ultimately transmitted to HHS, where it serves as the Agency's principal programmatic input to Administration resource allocation decision-making, as well as displaying the outcome of major policy development during the year. The plan is prepared each year by OPPE, with significant contributions by each BID and reviewed by major OD staff offices.

In addition to responding to the central NIH planning process, each BID has established its own structured planning process. Since the timing of the major events in the central planning process have been standardized over the years, the BIDs have been able to adjust their planning schedules in such a manner that the outcome of their planning processes serves as the principal source of input to the central planning process. This involves identification of future program directions, major proposed program initiatives, changes in emphasis, establishment of priorities and consideration of resource allocations within the context set by the OD planning agenda. While each Institute must consider many similar factors in planning its programs, there are also many differences. These differences in planning approaches can be attributed to the nature and scope of the research activity being planned, to the internal resources available, and to the individual planning requirements imposed by legislation, organizational behavior, and management style. The variety of planning approaches also reflects the great diversity and complexity in the many fields of inquiry that NIH supports and the processes through which knowledge is advanced.

In general, each Institute annually:

- Assesses its goals, objectives, and the research strategies designed to meet those goals;
- Reviews program progress, the state-of-the-art, evaluation studies, and various reports addressing particular program areas;

- Assesses scientific opportunities and plans program directions and emphases;
- Attempts to determine the national significance of the health problems under consideration;
- Reviews program contributions to broader health objectives established by PHS and HHS;
- Reviews responsiveness of programs to Congressional mandates; and
- Involves the Institute's National Advisory Council, as well as professional community, in establishing program directions.

These activities all influence the setting of priorities and result in a diverse array of planning documents and program reports. Consideration of these factors provides a basis for recommending program changes to the NIH Director as part of the central NIH planning process.

Director's Advisory Committee

The Associate Director for Program Planning and Evaluation serves as Executive Secretary for the Director's Advisory Committee (DAC), a public group advising on broad matters of health policy. In 1982, progress was made in restructuring and streamlining the Advisory Committee as a public forum for considering matters of health research policy. To assure a sharper focus in the Committee's deliberations:

- NIH identifies policy issues which require the development of proposals for decision-making.
- NIH staff conducts necessary research and develops policy options or position papers which characterize and clarify the issues and identify options. Through such efforts the DAC is given, at critical points in the policy formulation process, useful documents to consider, react to, and advise on.
- The agenda at a DAC meeting is limited, to the extent possible, to a single, major issue.

The structure under which the DAC operates has been modified to accommodate this role in the policy formulation process. Certain new features include:

- Inviting the participation of one representative from each BID Advisory Council at the DAC meetings. This assures linkages amongst advisory bodies in the policy development process and makes available a broader range of views to the Director, NIH.
- Establishing an issue development process at the NIH that involves active participation and collaboration between the Office of the Director and the Institutes in the identification of issues to be brought before the DAC and the development of options. Although a

small working group may be asked to carry primary responsibility for the development of a specific issue, all Institute Directors are given the opportunity to express their views.

This new role was first assumed by the DAC at its June 1983 meeting when the issue of the stabilization of research project grants was addressed and continued at its December 1983 meeting with consideration of a number of policy questions regarding NIH research training activities. In both instances, OPPE established small working groups to develop the specific issues. Planning, evaluation, legislative and program analysis functions were represented on these groups and provided essential participation in the collective shaping of positions requiring a variety of perspectives. All BIDs also participated in this effort through the review of documentation and modification of lines of inquiry.

Administration Planning Requirements

Both the PHS and HHS establish planning requirements for all agencies each year. The planning requirements, and their timing, are different at each organizational level and tend to change with changes in Administration. The central OD/NIH planning process, designed to first meet the Agency's needs, is managed and implemented with sufficient flexibility to also be responsive to PHS and HHS planning requirements. The PHS planning process consists of a series of structured sessions between the Assistant Secretary for Health and the Director, NIH, throughout the course of the year. All major OD staff offices participate in these sessions. The purpose of these sessions is:

- to review substantive program opportunities, priorities, and problems that will drive the subsequent development of the planning year budget and to discuss any legislative proposals under consideration;
- to agree on relevant policy issues requiring analysis during the year; and
- to assure that agency priorities have been developed within the general context of PHS priorities.

The planning agenda developed by OPPE is responsive to this set of considerations. Policy development tasks resulting from these considerations are identified, monitored throughout the course of the year and reviewed again in another structured session prior to the final development of the NIH Research Plan and the submission of the Preliminary Budget. Both the NIH Research Plan and the Preliminary Budget serve as source documents to the PHS and HHS as resource allocations are made for the planning year.

Summary of Factors Which Affect the OD Planning Function

There are many factors, both within and outside the NIH which directly affect the OD planning function. Their degree of influence may vary and the manner in which they are considered may differ depending upon which set of planning activities is involved. In general, these factors are:

- Congressional Actions--Authorizing legislation, mandates, directives and appropriations all directly influence research planning. The establishment of new Institutes, changes in research training legislation, proposals for small business set-aside, mandates to allocate a proportion of resources to a particular disease area, directions to develop a national plan, interest in providing greater support to an identified area of research or specific mandated studies are but a few examples of Congressional actions that influence planning. Obviously, the resources provided for program execution, as expressed through the appropriations process, directly affect research planning.
- Mission/Organizational Structure--The NIH is a health agency which carries out its mission through the conduct and support of biomedical research. The knowledge development process which characterizes the course of biomedical research does not always follow organizational lines, program boundaries, nor budget years. This phenomenon has clear implications for an OD planning function, requiring continuing attention to and planning for cross-cutting activities.
- Input from Constituency Groups--Interest groups, professional societies and organizations, lay individuals and the biomedical research community all play a part in the research planning process. This input can be expressed in a variety of ways, ranging from structured activities such as advice from the National Advisory Councils and the Director's Advisory Committee, planning subcommittees of these bodies, convening of special groups or task forces to consider a specific research area or health problem, to less structured interaction with representatives of these groups around specific issues.
- State of Knowledge--All planning for biomedical research proceeds from what is known about a health problem, life process or disease area and results in the identification of scientific opportunity, gaps and needs, rapidly advancing areas of research as well as cold or static areas, potential interventions ready for clinical testing and changes in direction, approaches or emphasis required to further advance the knowledge base.
- Social and Economic Burden of Illness--Incidence, prevalence, morbidity, mortality, health care costs are all factors, balanced with scientific opportunity and other factors, considered in planning program directions and change and in developing priorities.

- Existence of Adequate Research Resources--Trained manpower, adequate facilities and modern equipment and instrumentation are key to mounting and continuing a high quality biomedical research program. Constant attention must be given to such resource support during the planning process to assure their availability.
- Budget Decisions--Decisions made at the PHS and HHS level on the NIH budget throughout the course of the budget process impact directly upon research planning. As resource levels change, or emphasis shifted, research planning must respond.
- Other PHS Agencies--When major changes occur in other PHS Agencies, such as the dissolution of O.I.H., the NIH research planning process must accommodate and provide for these events. In addition, budget reductions or shifts in priorities in other PHS Agencies can affect NIH research planning to the extent that jointly funded/sponsored activities (such as the National Toxicology Program) are involved.
- Other Factors--Secretarial and White House priorities, OMB directives, reports of special commissions and task forces and media reports are all factors which impact upon research planning.

SECTION III--SELECTED POLICY CONSIDERATIONS

SELECTED POLICY CONSIDERATIONS

Introduction

In addition to the pressing need to achieve program balance through the judicious allocation of limited resources, the NIH must address an ever growing number of concerns which impinge upon its ability to carry out its generic mission.

This section discusses some of the major policy development activities that are underway in the Office of the Director, NIH. Rather than entirely new policy issues being raised each year, recurring issues and concerns tend to take on new or changing perspectives or gather additional impetus over time. The issues discussed here fall into this category and can be characterized as addressing problems and concerns which cut across organizational structures and individual program boundaries and have broad significance both within the Agency and the biomedical research community.

One problem of particular concern is the continuing physical deterioration of the Nation's research laboratories and the lack of access to advanced instrumentation required in much of today's sophisticated research. Efforts are underway to assess the magnitude of these needs and to develop strategies to meet them.

Increasing efforts to gain recognition and support for various areas of health research have created pressures which could significantly alter the structure and functions of the NIH. In response to these pressures a study is being conducted by the Institute of Medicine to analyze the evolution of the organizational structure of the NIH, examine current approaches in areas which cut across organizational lines, and suggest criteria for determining the need for change.

The use of animals in biomedical research plays a vital role in advancing our understanding of disease. The NIH is currently examining the policies and guidelines for the care and use of animals in research to determine their appropriateness and adequacy.

A continuing concern of the NIH is to assure an adequate supply of well-trained investigators to conduct biomedical research. New programs and policies have been designed to meet emerging needs and the area is under constant scrutiny to determine the adequacy of current efforts.

Recently, several initiatives have been taken to encourage and promote the participation of for-profit organizations in the support and conduct of biomedical research. The NIH is continuously monitoring the progress and effectiveness of these initiatives and is seeking ways to assure their success.

These concerns and imperatives are discussed, in detail, in the following section.

Research Infrastructure

Over the past decade, there has been growing concern over the deteriorating institutional base for health research. Most prominent in the concern is the growing obsolescence of research instrumentation and facilities in the Nation's research universities. Unless these major aspects of the concern are directly addressed, the rapid progress now occurring in biomedical research may be impeded and the momentum resulting from past investments jeopardized.

Extramural Construction

The NIH experience with construction authority for non-federal health-related research facilities dates back to 1948 when appropriations were made available to the National Cancer Institute (NCI) and to the National Heart Institute (NHI) for research construction. During the 35-year period since then, the NIH has had available a variety of authorities for construction of health research facilities and has spent approximately \$834 million for such purposes. Historically, Congress has been responsive to the need to maintain the Nation's physical plant for the conduct of health research. In the past 35 years, Congress has provided the NIH with nine separate authorities for the construction, renovation and/or replacement of health research facilities. Six have been repealed or terminated. Three of these authorities (NCI, NHLBI, NEI) are still active, although two (NHLBI, NEI) are not currently being used. In general, the following statements can be made about the authorities provided NIH and their use for construction, renovation, and replacement of health research facilities:

Legislative Authorities

- All but one of the authorities established have been for relatively specific purposes (construction, renovation, and replacement of cancer, eye or heart research facilities, mental retardation centers, primate research centers, medical library facilities). The sole exception was the Health Research Facilities Act of 1956 which provided a broader and more general authority, namely, the construction, renovation, and replacement of non-federal health-related research facilities with no limitation as to area of health-related research or type of facility.
- Almost all construction has been or is being funded under the grant mechanism. Several required matching support. For instance the Health Research Facilities Act directed a 50/50 matching grant program, and mental retardation centers and medical library authorities allowed for the Federal Government to cover only up to 75 percent of the cost of construction. Other authorities carried no such requirement.

Funding History

- Funds obligated by the NIH under all construction authorities during the past 35 years totaled \$834 million. Medical schools received the largest share of this support, approximately 55 percent. Since the termination of the Health Research Facilities program in 1968, \$243 million has been obligated for construction, or 29 percent of the total NIH experience. Nearly all of the funds obligated since 1968 have been for the construction and renovation of cancer research facilities.
- Early authorities for non-federal construction usually (although not always) carried their own separate appropriation; recent ones have not. Consequently, the funding of construction today tends to be placed more directly in competition with the funding of research. This, in large measure, accounts for the non-use of current authorities by the NHLBI and NEI, and a steadily declining amount of construction support by the NCI.

Needs Assessment

- None of the construction authorities were based upon a systematic and comprehensive analysis of need. Rather, expressions of need from the community(ies) tended to combine successfully with the political and economic forces of the time, leading to the enactment of the authorities and allocation of funds. Systematic assessment of need, when conducted, has occurred subsequent to the enactment of the authority.
- Based upon a review of existing documentation, it is reasonable to conclude that the need for construction, replacement, and major renovation of non-federal health-related research facilities is substantial and probably growing, although good, comprehensive measures of the extent of today's need do not exist. Highlights from these surveys and reports which seem most relevant are as follows:
 - After 1957, the federal government became a significant source of capital funds that built up the physical base for research. This reached a peak in 1965, when the federal government obligated more than \$142 million for R&D plants in colleges and universities. By 1974, federal funds for R&D plants had dropped to a low of \$29 million, a decline of 77 percent over the 1965-1974 period. Since 1974, with the exception of the NCI, there have been no major non-federal construction programs addressing needs in health research.
 - Approximately 60 percent of the health-related research space in use which was constructed during the period 1958-1968 was built with the assistance of the Health Research Facilities Program. This program was essential to developing the Nation's biomedical research capacity. It has been between 15-26 years since institutions received federal support under this program. During this time, research laboratory requirements have changed, brought about

by the growth in the knowledge base, the development of new technologies, more effective handling and processing of information, and requirements for higher standards. Research space of two decades ago, for the most part, cannot accommodate research requirements today without major renovation or replacement.

- In 1976, the American Council on Education, based upon a survey of 155 Ph.D. granting institutions, found that 29 percent of the health research space in use required replacement or renovation.
- Requirements for laboratory animal facilities were well documented in 1978 in a National Academy of Sciences (NAS) survey which found that 16 percent of all non-profit biomedical research organizations reported a need for replacement of space, 38 percent a need for remodeling, and 48 percent a need for additional space. In 1979, Princeton University did a small, informal survey of nine institutions and found that the need for facilities and large equipment in the next three years would be more than double the need in the past three years.
- In 1981, the Association of American Universities surveyed 15 leading universities and found an estimated \$765 million would be needed by these universities for research facilities and major equipment over the next three years just to sustain the current level of activity of existing faculty. These projected funding needs are almost double the level of expenditures over the previous four years.

Next Steps

- The realistic aim of any new construction authority should probably be for the renewal and maintenance of an adequate base for the Nation's health research effort, including new construction to replace outmoded facilities, to relieve overcrowding, to accommodate to changing research requirements, and for major renovation and repair of inferior facilities, rather than for any major new expansion. Currently, construction authority exists only for NCI, NHLBI and NEI. The rest of the BIDs, including DRR, have no such authority and cannot fund such activities. Consequently, if construction of health research facilities is to be seriously pursued, it will require the enactment of new legislation.
- Several months ago the NIH learned that two other agencies (Department of Defense and National Science Foundation) have been asked by the Congress to examine the state of university research facilities. The NIH has now joined with DOD, NSF, NASA, USDA, and the Department of Energy to plan a major survey covering all engineering, scientific and medical research facilities at academic and non-profit institutions. It is anticipated that a contract for the study will be let before the end of FY 1984. Research facilities will include construction, acquisition, renovation, modification, major repair or rental of space for use in scientific engineering or medical research and development.

Space will be defined as research operations space, controlled environment space (e.g., clean rooms, P3 laboratories), technical support space (media preparation, computer storage, special waste handling systems), research animal facilities, and research administration.

- To obtain very preliminary information on the magnitude of the problem, the agencies recently analyzed the five-year construction plans of 25 major universities and roughly estimated future needs. The future annual need for construction of research facilities at the 25 institutions is \$495 million as a lower bound. These institutions perform one-third of all academic R&D so the estimated total university need is \$1.4 billion using this preliminary measure.

Research Instrumentation

Experience has made it abundantly clear that instrumentation is at the core of experimental research. Modern instruments with expanded capabilities for analysis and measurement can open up entire new fields of investigation and can greatly reduce the time necessary to carry out experiments. For instance, the fluorescent activated cell sorter (FACS) provides a rapid and reliable method of distinguishing specific cell types from a mixture of cells and sorting them out for additional analytical studies. And nuclear magnetic resonance (NMR) spectroscopy has demonstrated its value as a powerful research tool which allows scientists to study patterns of regional nerve activity in the brain and to examine neurological structures that were not easily identifiable with earlier techniques.

The Problem

- The Nation's ability to expand the frontiers of knowledge depends upon access to modern equipment. Biomedical techniques are evolving so rapidly that a laboratory cannot be well instrumented once and remain so without constant updating and replacement. Increasingly, many of the scientists who work in university laboratories cannot obtain access to the advanced instrumentation that in large measure determines their ability to produce ground-breaking results. The costs of developing, purchasing, and maintaining instruments required for routine investigations have escalated at more than the cost of inflation. Moreover, such equipment-intensive fields as the biomedical sciences have experienced a decade or more in which instrumentation has become increasingly sophisticated and extremely expensive. During the same period, funds available for research instrumentation have declined considerably.
- It has been difficult to derive precise quantitative measures for assessing the severity of the problem; however, a number of studies suggest that the magnitude of the problem is substantial. On the basis of recent NIH program experience it is estimated that the NIH could award an additional \$20 million a year over the next five years in support of shared instrument grant awards alone to meet the highest quality research needs.

NIH Program Response

- To respond to the growing problem of obsolescence of research instrumentation, the NIH has attempted to achieve as much leverage as possible with existing funds for research resources by emphasizing funding mechanisms which encourage and promote the sharing of instruments, equipment, and facilities by investigators. Although the NIH research project grant mechanism provides reasonably well for relatively inexpensive equipment for use by individual grantees, a special need exists to provide support for large, expensive state-of-the-art instrumentation which can be shared by groups of investigators in pursuing research leads. In recognition of this increasing need:
 - The National Institute of General Medical Sciences (NIGMS) initiated a shared research instrumentation program for investigators holding research grants from that Institute. The award requires that at least 50 percent of the major users of the instruments purchased under this program be NIGMS grantees. The program provides for the purchase of items costing between \$30,000 and \$200,000.
 - The Division of Research Resources developed a shared instrumentation grant program for the purchase of equipment ranging from \$100,000 to \$300,000. These awards are made to NIH grantees who are located in institutions that are eligible to receive funds under the Biomedical Research Support Grants (BRSR) Program which provides institutions with support for activities that enhance the research environment. In FY 1983, the DRR also provided support for shared instrumentation through its Minority Biomedical Support Program.
 - The Division of Research Resources, through its Biotechnology Resources Programs (BRP) promotes the development of specialized equipment and advanced technologies and makes these modern resources available to investigators across the country.

Activity Underway

- The NIH has initiated a study of the status of academic research instruments (age, condition, capabilities, usage, etc.) and instrumentation needs in medical school laboratories. A collaborative arrangement with NSF insures that the study will provide data directly comparable to and contemporaneous with a larger study supported by NSF which is examining the same questions in university bioscience departments as well as instrumentation in other academic science fields. The results will provide further guidance for the size and scope of NIH instrumentation support programs. The status of the study is as follows:
 - A contract was signed with Westat, Inc., on September 29, 1983, to conduct the study.

- NIH has added three experts in biomedical research and instrumentation to the phase two advisory committee to the contractor.
- A stratified sample of 24 medical schools has been drawn, representative of total NIH-support to all U.S. medical schools. Letters were sent by the NIH Director to the deans of these schools encouraging cooperation. The NSF component of the study includes 198 biological science departments in a stratified sample of 42 universities.
- The survey was begun in March 1984. Questionnaire forms are being completed by 144 chairmen of medical basic science departments and the departments of medicine and by the chairmen of 198 biological science departments in graduate schools. Another questionnaire form is being completed by the principal users of each of about 2,400 medical school research instruments and 1,900 graduate school research instruments valued over \$10,000.
- A final report will be available by the end of September 1984.

Research Training

The National Institutes of Health sponsors basic and clinical biomedical and behavioral research to improve the health of the Nation. This mission involves supporting a broad range of activities that are part of the knowledge development process. A key component of this effort involves research training, a significant factor in providing for the future effectiveness of biomedicine. A continuing objective of the NIH is to provide support for a relatively constant number of trainees each year to assure the existence of adequate levels and types of skilled investigators to meet the biomedical research needs of the Nation.

Title I, the National Research Service Award (NRSA) of the National Research Act (Public Law 93-348), enacted by Congress in 1974, abolished and consolidated previous research training authorities of the PHS. The declaration of purpose in providing Federal support for research training is clearly stated in Section 102 where the Congress declared that:

- "(1) the success and continued viability of the Federal biomedical and behavioral research effort depends on the availability of excellent scientists and a network of institutions of excellence capable of producing superior research personnel;
- (2) direct support of the training of scientists for careers in biomedical and behavioral research is an appropriate and necessary role for the Federal Government; and
- (3) graduate research assistance programs should be the key element in the training programs of the NIH."

The NRSA is the sole authority under which the NIH supports the basic preparation of individuals for a career in biomedical and behavioral research.

Through a system of individual fellowships and institutional training grants, the fellow or trainee receives a stipend for full-time concentrated study and may elect, under supervision, an individual research focus. Funds are awarded for predoctoral and postdoctoral stipends and tuition, where warranted, with a modest allocation to the institution to defray training related expenses not covered by tuition.

Under the NRSA Title of the National Research Act of 1974, as amended, the National Academy of Sciences (NAS) is charged with conducting a continuing study of the national needs for biomedical and behavioral research personnel. Reports from the study are now published biennially and are submitted to Congress. The reports do not take into account the increasing needs of private industry, in particular those of the pharmaceutical or new biotechnology industries. It does, however, provide a useful starting point for estimates of research manpower needs and would appear to represent the minimum level required to keep the supply of investigators in balance with the Institutes' basic program needs.

Since 1977, the number of full-time research training positions budgeted for the NIH under the NRSA has been relatively stable, fluctuating between 9,654 in 1976 and 10,570 in 1983. For FY 1984 the NAS recommends that the NIH should support approximately 10,500 individuals.

Concern has been expressed that, in spite of the recent five percent increase in NIH stipends, the stipend level for NIH predoctoral trainees is not comparable to that offered by other agencies, and that M.D. postdoctoral stipends do not compete with salaries offered to Medical House Staff. NIH stipends for predoctoral trainees (\$5,292 raised to \$5,551) will still lag far behind the National Science Foundation (NSF) (\$8,100). NIH postdoctoral trainees will start at \$14,728 in FY 1985, about \$6,000 below comparable house staff salaries and far behind the \$24,500 paid by DoD.

Clearly, such discrepancies will make it increasingly difficult to attract the best students to the NIH training programs. NIH is now faced with the question of how to close the stipend gap without damaging the breadth of its existing research training programs. Recently it was decided that efforts to further increase stipend levels will be deferred until the 1986 budget process.

The application of scientific advances to maintain good health and prevent and treat disease is ultimately the responsibility of the physician. The trained clinical investigator is the critical link between the laboratory and health care provider. Despite the burgeoning of basic knowledge in the biomedical sciences, which has opened up vast opportunities for clinical research, the number of physicians seeking research training is below recommended levels. In addition, the percentage of total NIH grants that are held by M.D. investigators has dropped from about 35 percent in 1968 to approximately 23 percent in 1980. This appears to be the result of two trends. The most significant is a relative drop in the number of applications from physicians due to recent growth in the numbers of biomedical Ph.D.s making grant applications. M.D.s comprised about 30 percent of grant applicants in 1970 and only 24 percent in 1980. The second trend is the declining success of M.D.s in obtaining research project grants. Among new applicants, 50 percent of M.D. applicants obtained awards in 1974, whereas only 30 percent of M.D.s applying succeeded in 1980. Once approved, however, the funding rate of grants from M.D.s and Ph.D.s has been virtually the same. An adequate period of research training for physicians appears to make the difference between successful and unsuccessful applicants.

Among the reasons cited for the lower numbers of physicians in research training are:

- The average medical school curriculum contains little or no opportunity for laboratory experience.
- The debt load of medical students has grown enormously. While the average is approximately \$19,000, debts as high as \$30,000 upon graduation are not unusual.

- The NRSA research training stipend pays on the average \$6,000 per year less than does clinical specialty training.
- The growing sophistication of science and its professionalization in clinical departments requires that recipients of even the finest medical education and residency training spend a substantial amount of time, as long as three years, obtaining the necessary skills to be successful in research.
- Fewer practicing physicians are seeking research experiences to complement their specialty and subspecialty training.

A number of steps have been taken within the last few years to recruit and retain physicians for research careers:

1. Providing early exposure to research careers

- Short-Term Training. In FY 1980, the NIH initiated a program of short-term training to expose students in health professional schools early in their professional studies to the opportunities inherent in research careers. The program now supports more than 1,100 students a year during vacation or off quarter periods in approximately 70 schools of medicine, dentistry, pharmacy and veterinary medicine. It is hoped that this will be an effective recruiting device for the future and will continue to be supported as funds permit and strengthened as experience dictates.
- Post-Sophomore Fellowship. A short-term exposure to research, while serving as a satisfactory introduction, is probably less effective than a longer initial laboratory experience. The NIH, in the summer of 1982, therefore, modified one of its requirements for the appointment of individuals to research training grants. A student in a health professional school is now permitted to receive support if he/she interrupts his/her professional education for a year of research training without formally enrolling in a graduate school program. Research training program directors are encouraged to seek out the most highly qualified candidates for this appointment.

2. Strengthening ongoing research training and developing new opportunities

- The Medical Scientist Training Program. The most successful program for selecting and retaining clinical investigators has been the Medical Scientist Training Program (MSTP), supported by the National Institute of General Medical Sciences since 1964. This six-year program of study makes awards to 24 highly selected schools for students who simultaneously earn the M.D. and Ph.D. degrees. Followup evaluation has shown that 70 percent of the graduates hold positions in academic medicine doing research and engaging in the training of other physicians. The program now supports approximately 675 students per year.

3. Providing incentives for clinical research investigators

- Career Development Awards. The physician who has completed four years of medical school and one to three years of clinical training is, by and large, only modestly prepared with research skills. Even where successful participation in one or more research projects has taken place, the experience does not substitute for a planned program to develop research expertise. A substitute for a planned program to develop opportunity to qualified individuals with demonstrated research potential is now supported by the NIH in selected categorical areas of need.

The promising people selected for these advanced development programs contribute significantly to the body of new knowledge during the term of the award. Two mechanisms have been particularly successful in the attraction of physicians, the Clinical Investigator Award and the Special Emphasis Research Career Award. Both of these mechanisms provide for three to five years of supervised research development in areas of immediate interest to the funding institute. They provide up to \$30,000 per year in salary plus commensurate fringe benefits and some modest amount of research support.

- The Physician Scientist Award. The newest addition to the Career Development Award series was announced during the summer of 1983. The Physician Scientist Award is being supported by several of the NIH Institutes. The award is designed to provide five years of phased supervised research training. The first years of the research training experience will be obtained under the guidance of a sponsor, preferably in a basic science department. The award carries a salary equivalent to that earned by a member of the institution's house staff with equivalent experience, up to 10 percent of the basic science sponsor's salary and \$10,000 for research costs. The second phase, undertaken at a more independent level, will make up to \$20,000 available to cover research costs. The program is being initiated at a very modest level with the first awards being made by NIA, NIADDK, NIAID, NICHD, NIDR, NIEHS, and NHLBI. Other institutes are planning to offer the award as their budgets permit.
- The General Clinical Research Centers. The national system of General Clinical Research Centers (GCRC), supported by the Division of Research Resources, provides the principal milieu for clinical studies on hospitalized research patients and, in recent years, outpatients as well. An advanced clinical research development program, the Clinical Associate Physician (CAP) award, was first funded in FY 1975. This program enables outstanding clinical investigators to receive a guided research experience under the auspices of a GCRC Director. The experience involved two years of intensive work with clinical research patients. In FY 1982, the program supported 40 individuals.

These efforts to counteract the decline of the early 70's and to increase the supply of physician investigators may be contributing to an improved outlook.

During the past few years other aspects of the NIH training effort have been examined. The following are capsule summaries of some key activities.

- To attract physicians with research experience into research careers, we have increased our support of the K-series grants. Another initiative, now being planned to promote high quality training of clinical investigators, is an intramural NRSA program. The NIH also believes that increases are needed in the career development program at a rate of 200 added awards a year for three years.
- One of the principal recommendations of the National Advisory Research Resources Council Minority Biomedical Research Support (MBRS) retreat was that DRR seek training authority for the MBRS Program. This would give the MBRS Program additional flexibility needed to meet its goal of increasing minority participation in biomedical research. Anticipated uses of training authority would be for predoctoral fellowships for MBRS graduates and for faculty career enrichment awards. In some cases, the program may wish to initiate some undergraduate training programs, as a supplement to the current MBRS undergraduate research program. DRR staff is working closely with NIGMS and with outside consultants to develop the most rational and utilitarian program design for NIH. The first awards are expected to be made in FY 1985.
- The latest (1983) NAS report on "national needs" describes the beginning of their study of ways to foster the role of Ph.D.s in cooperative clinical investigation; the aim is to improve effectiveness and economy in clinical research. This may require curriculum modifications in the training of both M.D.s and Ph.D.s.
- The Director's Advisory Committee meeting, held December 14, 1983, focused exclusively on the subject of training and career development. There was considerable discussion of the need for incentives for clinical investigator training and of our current mix of manpower development mechanisms. The meeting has resulted in the identification of a number of areas in which additional data collection and analysis are needed.

The Care and Use of Animals in Research

The use of animals in biomedical research has played an important if not central role in advancing our understanding and treatment of disease. Countless lives, both human and animal, have been saved due to such advances. The scientific community believes the use of animals in research is eminently justified. In their quest to alleviate suffering caused by disease, scientists see a clear moral imperative behind the desire to learn the processes underlying normal and pathological biological phenomena.

Despite this justification and the record of achievements, the scientific community has been repeatedly challenged and questioned over its use of animals in research. Some critics of animal experimentation have maintained that all scientific investigations using animals should cease. Others have proposed less extreme, yet restrictive, measures.

From the NIH perspective, it is feared that: (1) public confidence and support of biomedical research will be eroded, (2) inappropriate restrictions will be placed upon the use of certain species and techniques, and (3) unnecessary and counterproductive reporting or oversight requirements will be mandated. The net result of such actions would be a stifling of scientific freedom which would ultimately retard medical progress.

Over the years, the NIH and the scientific community have demonstrated a commitment to the humane treatment of animal subjects. Such care has been motivated both from a moral as well as a scientific perspective. It is widely acknowledged in the biomedical community that quality animal care is synonymous with good science.

This should not be interpreted to mean that animals used in laboratories never undergo stressful or painful procedures. While it is true that many experimental animals are never subjected to adverse conditions, others are. In the study of disease processes, pain, and trauma, scientists must sometimes model deleterious events. In such cases, however, responsible investigators work diligently to insure that animal distress is kept to a minimum.

In response to the questions and criticisms that have been raised, the NIH has reexamined the adequacy and effectiveness of existing policies. Although the mechanisms currently in place to safeguard the welfare of research animal subjects have worked well in the past, opportunities for improvement are being pursued. The following is an overview of current activities which are directly related to the care and use of laboratory animals.

- The NIH sponsored a National Symposium on the imperatives in the use of laboratory animals in health research. The two-day meeting addressed Public Health Service concerns, policies and procedures for ensuring humane care and use of laboratory animals involved in research conducted and supported by the PHS. The forum sought to develop a broad consensus among the research community and the public

at large. The symposium, held April 11-12, 1984, was attended by members of the scientific community, congressional staff, representatives of academia, the press, industry, the public, and employees of other Federal agencies.

The Office of Protection from Research Risks (OPRR) had the lead role in organizing the symposium. This meeting was the first phase of four educational initiatives being undertaken by OPRR. The other activities include: (1) the development of a series of regional workshops; (2) the creation of a handbook for animal care committees; and (3) the development of a variety of audiovisual materials for self-tutorial exercises as well as for the support of lectures, workshops and demonstrations.

- The Guide for the Care and Use of Laboratory Animals is being revised under a contract with the Institute of Laboratory Animal Resources of the National Academy of Sciences. This year, public hearings were incorporated into the revision process. The revised Guide should be available by September 1984.
- NIH officials have conducted a series of site visits at ten randomly selected sample institutions to assess the extent of compliance with principles set forth in The Guide for the Care and Use of Laboratory Animals. A report on the findings has been completed and published in a special edition of the NIH Guide for Grants and Contracts, Vol. 13 No. 5, April 5, 1984.
- A memorandum of understanding between NIH, USDA and FDA has been developed. All three of these agencies have responsibilities in the use of animals in research and testing activities. The memorandum of understanding will facilitate communication and cooperation between these agencies.
- The Interagency Primate Steering Committee has been restructured and is now titled the Interagency Research Animal Committee (IRAC). The Committee will serve as a focal point for federal agencies to discuss issues involving the care, use, and conservation of all animal species needed for biomedical research and testing.
- The Trans-NIH Coordinating Committee on Research Animal Resources serves as a point of NIH coordination, allowing information related to the care and use of research animals to flow across institute lines.
- A draft revision of the PHS Policy on the Humane Care and Use of Animals (used for extramural programs) has been developed at NIH and is currently undergoing review. Public input regarding the proposed revisions is being sought.
- The NIH Animal Care Committee has developed a Manual Issuance on the Care and Use of Laboratory Animals for the Intramural Program at NIH. These guidelines will help assure uniform and high quality animal care and use practices in the intramural programs.

- The Division of Research Resources has awarded a contract to the National Academy of Sciences (NAS) to evaluate various types of biomedical models and methods which do not use animals, or use only lower forms of animals. The NAS contract was begun late in July 1983, and will run until the end of January 1985.
- The issue of the care and use of laboratory animals will be the subject of the forthcoming NIH Director's Advisory Committee meeting. The meeting is scheduled to take place in June 1984.

Legislative Activity

Legislation related to the use and care of animals in federally supported research has been concerned primarily with two issues: (1) finding methods of research and testing which eliminate or reduce the use of animals or use less painful procedures and (2) assuring that proper care and humane treatment of animals are provided.

In the 98th Congress, five bills and one resolution have been introduced which deal exclusively with this issue. Provisions relevant to the use of research animals are also included in H.R. 2350, the NIH reauthorization bill.

- On March 2, 1983, Senator Robert Dole (R-Kan.) introduced S. 657, the Improved Standards for Laboratory Animals Act, an amendment to the Animal Welfare Act; applicable to all federally supported research laboratories. The bill would upgrade standards for care and treatment of animals and establish requirements for institutional animal care committees and for increased reporting to the USDA Animal and Plant Health Inspection Service (APHIS) and the Federal funding agency. In addition, S. 657 would eliminate current Animal Welfare Act limitations on APHIS inspection of laboratories where research is in progress. This bill was referred to the Committee on Agriculture, Nutrition, and Forestry. On July 20, Senator Dole chaired a hearing of that Committee, to discuss S. 657. Dr. William E. Raub, NIH Deputy Director for Extramural Research and Training, and Mr. Bert Hawkins, Administrator of APHIS, testified for the Administration. There has been no further action on the bill.
- On March 24, 1983, Senator Orrin Hatch (R-Utah) introduced S. 964, the Animal Welfare in Research Study Act of 1983, for himself and Senator Edward M. Kennedy (D-Mass.). The bill would require the Secretary of Health and Human Services to arrange for a study of the care and use of animals in research, possible alternatives to animal use, and current relevant laws, regulations, and guidelines. In addition, Senator Hatch requested that the Office of Technology Assessment initiate a study of alternatives to animal use, and report to the Congress. S. 964 has been incorporated into S. 773, the NIH reauthorization bill. S. 773 is pending full Senate action.

- On April 20, 1983, Representative Brian Donnelly (D-Mass.) introduced H.R. 2633, to promote development of research, experimentation, and testing methods that minimize the use of, and pain and suffering of, live animals in research. This bill has been referred to the Committee on Science and Technology.
- On April 21, 1983, Representative Tom Lantos (D-Calif.) introduced H. Res. 170, to promote proper treatment of laboratory animals and to recognize the efforts of the organization, Mobilization for Animals. H. Res. 170 has been referred to the Committee on Post Office and Civil Service.
- On May 26, 1983, Representative James J. Howard (D-N.J.) introduced H.R. 3170, to establish a Commission on Modern Farm Animal Practices. The Commission would consider recommendations from NIH (and others) regarding research on potential human health hazards related to intensive farm animal husbandry. This bill has been referred to the Committees on Agriculture and Energy and Commerce.
- Provisions in H.R. 2350, the NIH reauthorization bill, related to care and use of laboratory animals include:
 - requirement for an NIH research plan regarding research methods which eliminate or reduce the use of animals or produce less animal pain and distress;
 - requirement that the Secretary promulgate guidelines for proper care and treatment of research animals and for organization and functions of institutional animal care committees;
 - requirement that institutional animal care committees review and report on all animal study areas and facilities at least semi-annually;
 - requirements that the NIH Director issue guidelines for necessary information about animal care, treatment, and use, to be included in all applications for research support, and that research support be suspended or revoked if institutions fail to comply with standards;
 - requirements that the Secretary, through the NIH Director, arrange for a comprehensive study, by the National Academy of Sciences, of the use of animals in research and a report to Congress on that study, including recommendations for legislative or administrative action.

This bill was passed by the House on November 18, 1983.

- On March 8, 1984, Representative Robert G. Torricelli (D-N.J.) introduced H.R. 5098, to promote the dissemination of biomedical information and to prevent duplication of research with live animals. The bill would provide for the establishment of a National Center for

Research Accountability at the National Library of Medicine, to conduct a comprehensive, full-text literature search to assure that a proposed project is not redundant research, before Federal funding of any research project using nonhuman vertebrates; for the training of biomedical information specialists in use of modern technologies; and for the dissemination of full-text articles to medical libraries at reasonable cost. H.R. 5098 has been referred to the Committee on Energy and Commerce. .

The NIH Organizational Structure

Background and Introduction

During the past 25 years a significant number of proposals to change the organizational structure of the NIH, through the establishment of new institutes and the transfer in of existing organizations, have been made. The preponderance of these proposals have surfaced in legislation, stimulated by a combination of congressional interest and constituent group advocacy.

Although this period has been filled with much activity dedicated to establishing new institutes at the NIH, the basic organizational structure of the agency has remained remarkably stable during this period. Two major, permanent changes (establishment of the NEI and NIA) have occurred which the NIH opposed at the time. Other significant changes have also occurred during this period (creation of divisions, elevation of divisions to institutes, change in institute status and/or title), either at the initiative of the NIH or in response to pressure for change. Several transfers of major organizational components both into and out of the NIH structure have also taken place during this period.

Summary Findings

In general, the following statements can be made about proposals to change the organizational structure of the NIH:

Proposals for Change

- Since 1959, proposals have been made for the establishment of approximately 45 new institutes at the NIH. Thirty new institutes were proposed through the legislative process; 15 have been promoted through a variety of other channels. In addition, four major existing organizations have been proposed in recent years through the legislative process for transfer to the NIH. The net result has been that five new institutes were actually established, namely, the NICHD, NIGMS (previously a division), NIEHS (previously a division), NEI, and NIA. Four were established legislatively, NIEHS was created administratively.
- During this period, the 30 new institutes that have been proposed through the legislative process have been introduced in approximately 178 separate congressional bills. While most of these proposed institutes died in the legislative process, two which the NIH opposed at the time did survive and resulted in the establishment of the NEI (80 bills) and the NIA (9 bills).
- Of the 178 bills introduced, 32 reached the level of serious consideration where they were brought up and discussed in committee, involving the proposed establishment of 11 new institutes. Since rule changes were put in place in the House in the late 1960s allowing cosponsors

to a bill rather than requiring the introduction of identical bills, the number of new institutes proposed has remained steady. Despite a preponderance of legislatively proposed institutes being introduced in many bills over the past two and one-half decades, the Congress has accorded the NIH a reasonably stable organizational structure during this time.

- The NIH reauthorization bill currently under consideration by the Senate proposes two new institutes, an Arthritis Institute and an Institute of Nursing.
- During this period, several organizations were transferred from the NIH, namely, the Division of Biologic Standards (DBS) and the National Institute of Mental Health (NIMH), while the Division of Regional Medical Programs (DRMP) and the Bureau of Health Manpower (BHM) were reassigned to NIH only to leave somewhat later. The principal concern leading to their transfer out related to the extent to which these organizations' missions belonged within the NIH structure. All organizations were removed from the NIH as a result of administrative action exercised by the Secretary under existing authorities. The Secretary has the authority to create new institutes and to transfer or abolish organizations originally created through administrative action. The Secretary also has the authority to transfer organizations created by law if the enacting legislation does not specify their exact location (for example, creates within the Public Health Service). If the current House reauthorization bill for NIH is enacted, this authority will be limited in the sense that all NIH institutes will be authorized in law at the NIH.
- Although the basic NIH organizational structure has remained reasonably stable over the past two decades, there has been significant change within that broad structure. Last year alone there were 47 organizational changes in the BIDs' intramural structure. Any serious analysis of the NIH organizational structure should consider the extent of change below the BID level, and the extent to which such changes are responsive to knowledge development and its application to health problems.
- Several proposals for new institutes (National Institute on Trauma and Institute of Nursing) have received reinforcement from special reports prepared by the National Academy of Sciences, namely, its 1966 white paper on Accidental Death and Disability: The Neglected Disease of Modern Society and the recent IOM report on Nursing and Nursing Education: Public Policies and Private Actions. The former recommended expansion within the PHS of research in shock, trauma, and emergency medical conditions, with the goal of establishing a National Institute of Trauma, while the latter recommended that the Federal Government establish an organizational entity to place nursing research in the mainstream of scientific investigation. Congress recently directed the National Highway Safety Administration to commission the Research Council of Life Sciences and the Institute of Medicine to establish a

joint committee to study the state of trauma and to suggest organizational arrangements to address the problems. The Senate reauthorization bill proposes the establishment of an Institute of Nursing.

- Past major studies of the NIH conducted by outside commissions or panels have endorsed the broad categorical structure of the NIH. The most recent completed study by the 1976 President's Biomedical Research Panel made it clear that the creation of additional institutes at the NIH is not an effective approach. Since then, there have been legislative proposals to establish nine new institutes and transfer in four other organizations. To what extent these studies may have influenced the outcome of the legislative proposals would be difficult to assess; however, it seems clear that these studies have not proven harmful to the NIH organizational structure.

Rationale for Change

- The arguments for establishing new institutes have been well stated over the years and are strikingly similar, although each has its unique characteristics. The burden of proof regarding the validity of these arguments often falls on the NIH rather than the proponents of a particular proposal. Rationale put forth for new institutes tends to cluster around two areas:
 - scientific
 - to enhance identity and focus for specific disease, process or organ system
 - to meet gaps in research
 - to promote greater career interest in neglected areas
 - to respond to demographic or epidemiologic changes
 - management
 - to achieve greater coordination of research
 - to increase the resources allocated to a particular area, and to biomedical research in general
 - to increase public accountability and accrual of economic benefits
 - to achieve parity with other disease areas
- The arguments opposing the creation of a new institute have also become well established over time. Once a new institute is established however, it becomes the responsibility of all parties to assure its success and to minimize disruption to and potential negative effects on ongoing activities. Given this reality, it becomes more

difficult later on to convince proponents of the harmful effects of establishing new institutes. Rationale opposing new institutes tends to cluster in the same two areas:

-- scientific

- research in one area should not be removed from the broader research continuum; research should not be isolated from the mainstream of integrated, multidisciplinary programs
- research needs are being met through current structure; limiting factors are those of trained manpower and sound research ideas
- growth and support for a given research area reflects the quantity and quality of research proposals received

-- management

- new institutes add significant administrative costs which takes funds away from research and are disruptive to ongoing programs
 - proliferation of institutes damages the agency's ability to administer biomedical research effectively and encourages other special interest groups to lobby for their interests
 - economic conditions do not allow for expansion; new institutes would be established at the expense of ongoing activities
 - sufficient legislative authority exists to permit the agency to meet changing needs without altering its organizational structure
- Effective approaches in the past for responding to serious proposals for new institutes have included both opposition to the proposal coupled with acknowledgement of and substantive accommodation to the problems/issues raised. Sickle Cell, population and lung proposals best typify such an approach. Some actions which the NIH has taken in response to proposals to create new institutes include:
 - elevating the organizational status of selected programs, divisions or institutes, creating senior level positions, and changing the name of an institute
 - developing national plans to deal with specific health research concerns, submitting special reports to Congress, and conducting studies of issues raised
 - establishing centers or special programs and establishing coordinating committees

Factors Contributing to Pressure for Change

- In the past 25 years, the NIH has been recognized as the most successful, and probably the least controversial agency in the DHHS. As the NIH has evolved, its research activities have touched upon an ever greater number of diseases, health problems, organ systems and biological processes. A great number of these are not reflected in the formal program or organizational structure but are dispersed throughout or embedded in a broader set of activities. There is no comparable organizational structure in the PHS or DHHS where such diverse and numerous interests are addressed. Occupying a visible place in the organizational structure of the NIH is seen by public and special interest groups as providing assurance for even greater success. These views are not likely to diminish in the future; as resources remain constrained, they may become more intense.
- Some significant changes in the manner in which Congress operates have occurred during the past fifteen years. Reforms adopted by the House of Representatives in the early 1970s weakened the power of standing committee chairs while strengthening the role of subcommittee chairs in the legislative process. Standing committee chairs lost the power to appoint subcommittee chairs, to control referral of legislation to subcommittee, to prevent their committees from meeting, and to control the management of legislation in specific areas. It is no longer possible for an agency to control its destiny through negotiation with a few congressmen, and legislative access by special/single interest groups has been enhanced significantly; consequently, proposals to establish new institutes are not as difficult to bring up for consideration.

Study of the NIH Organizational Structure

The 97th Congress, both the House and Senate, introduced H.R. 6457, the Health Research Extension Act of 1982. One of the provisions of this Act would have created a National Institute of Arthritis and Musculoskeletal Diseases and at the same time directed the Secretary, DHHS, through the Director, NIH, to "arrange for the conduct of a study of the effectiveness of the existing combinations of disease research programs within the individual national research institutes and of the standards which should be followed in establishing new or realigning existing national research institutes." The Act further directed the Secretary to request the National Academy of Sciences to conduct the study, for the Department to fund the study, and for the NAS to deliver a final report 18 months after the initiation of the study.

In November 1982, at the 1985 PHS Planning Session, the Assistant Secretary for Health requested the Director, NIH, to initiate a study of the organizational structure of the NIH even if the pending legislation was not enacted, and to request the NAS/IOM to conduct the study. The Director, NIH, agreed at that time that such a study was timely and that the expertise represented by the NAS/IOM was crucial to the successful conduct of a study of this magnitude and visibility. These agreements were subsequently reaffirmed in discussions between the Director, NIH, and his OD staff and BID Directors.

Study Objectives

In April 1983, the NIH signed a contract with the NAS/IOM to make an independent objective study of the organizational structure of the National Institutes of Health (NIH) and considering scientific developments and economic conditions recommend the establishment of the criteria (standards) to be met for determining the need for any substantial change in the organizational structure of the NIH. The IOM was asked to perform the following four inter-related tasks:

- Analysis of organizational evolution--conduct a thorough, systematic review of the agency's organizational evolution and development. This analysis will include a review of the organization's development and an examination of the contributing factors involved in such development. The present organizational structure and the underlying rationale for this structure will also be examined.
- Current organizational analysis--examine the present approach to those issues which cut across organizational lines. The IOM will examine the basis for the current methods of handling such issues and develop alternative approaches for consideration. The rationale for and implication within the current NIH structure of all approaches (current and alternatives developed) will be analyzed.
- Study recommendations--considering scientific developments and economic conditions, the IOM will develop rationale and criteria to be met to determine the need for change, in any substantial manner, the organizational structure of the NIH, and determine possible alternative organizational structures for the NIH.
- Briefings--between November 1, 1984, and December 16, 1984, following the public release of the report, NAS/IOM staff and steering committee members shall be available to provide briefings to Administration, Congressional and private sector groups and shall stand ready to respond to requests for more information about the study's findings.

Study Structure

The IOM implemented the study by establishing a Steering Committee of highly qualified scientists, scholars, management experts and representatives from industry. The Steering Committee named three panels to examine certain aspects of the study, as follows:

- Panel 1--Historical Issues--This panel will examine the evolution of NIH's mission and organizational structure in order to shed light on the purpose of the current structure and its reaction to organizational change. This will involve gathering information on when, why, and how new institutes were started, the flow of funds to new and remainder institutes, the effect on science, and the effect on management. The panel will also examine organizational changes below the institute level, including program structure and mix of research mechanisms. It will also include a study of changes in the political

climate, and the relationship between NIH, the Department of Health and Human Services, and the Congress.

- Panel 2--Current Organization--This panel will examine the current organizational structure of the NIH and related research agencies and explore a number of management issues that cut across organizational lines. This will include an analysis of the span of the Director's control, the program planning process in each institute and the Director's office, staffing profiles, and the composition and role of study sections and advisory councils, and the role of staff and the role of advisors. It will also include studies of the organization and mission of agencies that have been proposed as additions to NIH so that the committee can develop criteria about whether or how they should be incorporated into NIH.
- Panel 3--Alternatives--This panel will examine alternatives to the current organizational structure, especially in regard to goal setting, decision making, priority setting, and budgeting. This will include a discussion of (1) "scientific opportunity" and "burden of illness" as criteria for setting research priorities; (2) the balance between basic and targetted research; (3) the balance between intramural and extramural research; (4) the balance between funding mechanisms, such as grants and contracts; and (5) how to promote and stimulate priority or neglected research areas. The panel will explore these issues in part by an examination of other research institutions, such as the NSF, foreign medical research councils, and industrial labs. Although the panel will be cognizant of political realities, it will attempt to search for alternatives to the current structure for evaluation by the full committee.

The study is on schedule and a final report is expected in October 1984.

NIH/Industry Interaction

Recent initiatives have encouraged greater interaction between government agencies and commercial organizations and have opened the way for new partnerships to form, promoting improvement in the health of the Nation. The NIH has taken advantage of recent opportunities to establish closer relations with the private sector and is actively involved in seeking additional mechanisms to pool resources. This paper will describe some of the actions that have been initiated to stimulate and facilitate NIH/Industry cooperative activities.

History

In 1962 the Department of Health and Human Services (HHS) adopted a general policy which restricted the award of research project grants to non-profit institutions and required the use of the contract mechanism for the support of activities conducted by for-profit organizations.

In 1982 the policy concerning the use of research support mechanisms was modified to make for-profit organizations eligible for research grant support. This new policy was widely promulgated to encourage the submission of research grant applications from private industry, and the NIH actively sought nominations for additional scientists from the industrial sector to serve on its peer review groups.

In the short time since the implementation of this new policy there has been a modest, but important, re-entry of commercial organizations into the fold of NIH grantees. For example, in FY 1982, NIH received through the standard research grant process only 12 applications from for-profit organizations and three awards were made from this pool. In FY 1983, the group of applicants grew to 67, of which 13 were funded.

While involvement of the private industry sector continues to be encouraged through the standard research grant process, additional means are being sought to encourage and promote such participation.

Small Business Innovation Research Program

In 1982 the Congress passed and the President signed into law the "Small Business Innovation Development Act" (P.L. 97-219) which requires Federal R and D agencies to set aside a portion of their extramural budgets for Small Business Innovation Research (SBIR) Programs. The program is intended to promote technological innovation within the small business community, provide the small business sector an increased role in Federal R&D, encourage private capital to commercialize the results of federally funded research, and foster and encourage participation of minority and disadvantaged persons in technological innovation.

In order to meet the definition of a "small business," a firm must be independently owned and operated, the number of employees may not exceed 500, and the company must be located in the United States and owned or controlled by United States citizens. A firm may also qualify for the SBIR program if it is owned by women, minority, or disadvantaged persons.

As the lead agency for the PHS, the NIH works to assure that SBIR policies and procedures are implemented in a manner that is consistent with both the enabling legislation and pre-existing agency mission requirements. The NIH also coordinates the SBIR activities of the PHS with the Office of Small and Disadvantaged Business Utilization, HHS, which has oversight responsibility for all of the HHS activities in this area.

Each year, the PHS issues an Omnibus Solicitation to invite so-called Phase I grant applications from small businesses that have the technological expertise to contribute to the R&D mission of the PHS agencies and offices participating in the SBIR Program. The objective of Phase I is to establish the technical merit and feasibility of proposed research efforts that may ultimately lead to commercial products or services, and to determine the quality of performance of the small business awardee organization. In FY 1984, the PHS will grant approximately 80 Phase I awards, each not to exceed \$50,000 (including direct and indirect costs) for a period normally not to exceed 6 months.

If an evaluation of efforts funded under a Phase I award demonstrates enough progress to justify further Federal investment, the firm may apply for Phase II awards. These grants may not exceed \$500,000 or a two year time period unless agency needs or research plans require exceptions.

The objective of Phase III is for the small business to pursue with non-federal funds the commercialization of the results of the research funded in Phases I and II. This requires a firm commitment of support from industry. Although it is too early to judge the success rate of participants in the PHS SBIR program, grantees of the more established National Science Foundation SBIR program have been able to attract substantial interest from the private sector. Evidently, large firms tend to show a degree of confidence in smaller firms that have demonstrated the ability to win SBIR grants. Phase III may also involve follow-on non-SBIR funded R&D or production contracts with a federal agency for products or processes intended for use by the U.S. government.

Applications for SBIR awards are reviewed through a process that follows closely that which is employed in the review of regular research grants. However, the study sections responsible for the initial review of applications for technical merit are specially constituted to include scientists and other technical experts from the small business community. The applications are judged for (1) soundness and technical merit of the proposed approach; (2) qualifications of the proposed investigator, supporting staff, and consultants; (3) potential of the proposed research for technological innovation and commercial application; (4) appropriateness of the requested budget; and (5) adequacy and suitability of the facilities and research environment.

With approval of the Small Business Administration and the Office of Management and Budget, the NIH has modified the original Federal SBIR program to meet the needs of its applicants. For instance, applications are now reviewed three times each year, rather than once, following the schedule developed in the extramural grants program. The NIH has also developed a simpler application form and condensed the instruction form. In addition, the

Small Business Administration has agreed to a standard NIH policy requiring cost-sharing by grantee organizations. Finally, the executive secretary to each study section prepares a summary statement following the grant review that provides valuable feedback to the principal investigator.

In the SBIR Program, interaction between NIH and industry is limited to the grant award process. Other activities involve a greater degree of communication between government and industry representatives both in the initiation and the actual performance of research projects. The following section describes the activities of a committee charged with the responsibility to develop a general set of principles governing NIH-private sector endeavors.

Committee on Joint NIH-Private Sector (Industry) Endeavors

The BIDs, at various times and for various purposes, have established joint endeavors with commercial organizations to accomplish specific health research goals. For example: (1) pharmaceutical companies have provided drugs to NIH investigators (or to NIH-supported investigators) for toxicological, laboratory or clinical testing; (2) BIDs and commercial organizations have jointly sponsored clinical research activities in multi-center studies through the direct provision of funds, personnel, equipment, supplies, or services; and (3) BIDs and commercial organizations have jointly sponsored conferences or produced public information materials.

The relationships and agreements between NIH and the cosponsor(s) have depended on a number of important factors which have included (1) specific programmatic needs of the BID, (2) potential public health impact, (3) stage of development of a drug or commercial product, (4) the product, and (5) the relative levels of support provided by the NIH and by the cosponsor. Until the present, there has existed no NIH-wide procedure for delineating the extent and nature of these relationships.

In April 1983, at the request of the Director, NIH, the Deputy Director, NIH, established a Committee on Joint NIH-Private Sector (Industry) Endeavors to deal with the legal and policy issues which affect joint ventures with the private sector. The Committee identified a number of issues that must be considered by NIH staff when establishing joint endeavors with commercial organizations. These include (1) the programmatic importance of the project to NIH, (2) the reasons for pursuing outside support (or for not supporting the project completely with NIH resources), (3) the scientific integrity of a jointly-sponsored research project (e.g., data management, quality control, decisions to modify protocol, release of study results), (4) the integrity of the NIH (e.g., implied endorsements or advertisements), (5) the accuracy of scientific information to be disseminated, and (6) legal and policy issues (e.g., patents, gifts, solicitation of contributions, conflicts of interest, peer review).

These "principles" are not intended to limit the types of joint ventures NIH staff might pursue. Rather, they have been developed in order to highlight some of the issues which NIH staff should consider. In some cases, it will be necessary to develop formal written agreements with cosponsors which define the responsibilities of the various parties--the NIH, cosponsors, performers. In other cases, such as extramural projects, many of the relationships will already be documented by grant or contract awards and will be

governed by existing NIH policies and procedures. In still other cases, NIH staff might determine that formal agreements would disrupt or hinder a particular joint venture and, in the interests of accomplishing NIH goals, the joint endeavor might be pursued with informal arrangements between industry representatives and NIH staff.

The Committee is preparing an Information and Instruction memorandum to aid NIH staff involved in initiating ventures in tandem with for-profit organizations. One example of such an activity--the conduct of clinical trials--is provided in the following section.

Clinical Trials

NIH actively solicits the cooperation of the private sector in the conduct of clinical trials. Clinical trials are the final step in the testing and validation of medical interventions, and ideally, should be performed on each new preventive or therapeutic modality before its introduction into clinical practice. A scientifically rigorous trial, however, is so costly in funds and personnel and time consuming that this ideal cannot be realized for each medical innovation. Consequently, they are mounted only for those of the greatest importance and potential applicability. These characteristics create a problem because clinical trials, while essential to the timely transfer of knowledge to medical practice, must compete for funds with other clinical and laboratory research demands. In response to this problem, NIH is seeking greater collaboration with private industry in the conduct and support of clinical trials and is exploring alternative or complementary approaches to the collection of data traditionally gathered through clinical trials.

Office for Medical Applications of Research (OMAR)

The NIH Office for Medical Applications of Research provides another channel for communication between NIH and the private sector. The NIH considers the assessment of biomedical technologies and the transfer of the results of such assessments to practitioners as a critical activity. The Consensus Development Program is a major and highly successful vehicle for carrying out this objective. These programs, frequently cosponsored by OMAR and one or more Institute, convene a panel of experts from government, industry and academia, and are held for the purpose of discussing and comparing new and traditional therapeutic modalities. The results of these conferences on such topics as liver transplantation, analgesic nephropathy, and dental sealants in the prevention of tooth decay are widely disseminated. In addition, OMAR coordinates assessments of drugs, devices and procedures by NIH scientists which in turn are used by the Office of Health Care Technology (PHS) in providing recommendations to the Health Care Financing Administration on the reimbursement of these technologies under Medicare.

NIH also participates in efforts undertaken at the White House level to facilitate government interactions with industry. One significant contribution is described in the next section.

White House Science Council Federal Laboratory Review Panel

In March, 1982, the White House Science Council's Federal Laboratory Review Panel was appointed to examine the 700 Federal laboratories and to recommend actions to improve their use and performance. The Panel was specifically charged to look at laboratory missions, identify any systemic impediments to performance, and determine whether the public investment in research is achieving a maximum return.

The Federal Laboratory Review Panel issued its report (commonly referred to as the Packard Report) in May 1983. At the President's request, the Federal Coordinating Council for Science, Engineering and Technology established a Committee on Federal Laboratories to monitor implementation of the recommendations proposed in the Packard Report. The Associate Director for Intramural Affairs, NIH, is a member of this Committee, and has contributed the NIH perspective and experience in meeting the goals described in the Report. In addition, NIH has benefitted from learning about similar efforts within other agencies.

One of these recommendations was that "R&D interactions between Federal laboratories and industry should be greatly increased by more exchange of knowledge and personnel, collaborative projects, and industry funding of laboratory work." NIH provided the following selected highlights of agency accomplishments for inclusion in the Committee's draft progress report. Through July 1983, some 54 non-exclusive licenses and an additional 10 exclusive licenses were granted to industry for patented inventions made in NIH laboratories. Conversely, a recent agreement between the National Cancer Institute and an industrial biotechnology firm will permit NCI to explore industrially developed technology in Federal cancer research programs.

The authority to grant these licenses and issue patents for products or processes developed in Federal laboratories stems from legislative modifications mandated in the Patent Reform Act of 1980. This change in government policy is but one of many that have enabled NIH to establish a wide variety of mutually beneficial relationships with industry. The NIH is currently investigating other policy changes that will stimulate cooperative ventures between NIH scientists and industry. The NIH policy regarding outside work, i.e., work performed by a government scientist in his private capacity and on his own time, is being examined for possible revision to allow "consulting" for profit-making companies. The potential impact of any changes in NIH policy will be carefully assessed, since close interaction between government, academic and industry scientists, each operating under different personnel policies, will inevitably lead to delicate and sensitive situations.

In conclusion, NIH is actively involved in reviewing practices which have inhibited interaction with industry in the past, and seeking ways to correct these situations as they become known. Already, extensive cooperation between NIH and members of the scientific community, both in industry and academia, is fostered through the intramural and extramural programs. In times of fiscal restraint, everyone benefits from increased cooperation. Through several ongoing projects, it is anticipated that such activities will increase. In addition, NIH will continue to seek ways to clarify existing policy and initiate further joint activities with industry in order to maximize the return on the public investment in biomedical research.

SECTION IV--SUMMARY OF BID PROGRAM OPPORTUNITIES

NATIONAL INSTITUTE ON AGING

I. Major Program Changes, FY 1986

● Aging

Research efforts will be expanded in a number of important areas in FY 1986, including Alzheimer disease and molecular genetics, and in the investigation of specific problems of the elderly such as urinary incontinence, osteoporosis, falls and hip fracture. Some expansion will also occur in the assessment of health and effective functioning and in studies of the rapidly growing population over age 85. The additional competing awards which will support these efforts will include grants under the Teaching Nursing Home Program, the Alzheimer Disease Research Centers, the Clinical Trials of Behavioral Therapies for Urinary Incontinence, and a Behavioral Sciences Research Program initiative on the "oldest old," as well as other NIA grant programs.

Present epidemiologic investigations will be broadened by the implementation of studies on aging-related changes in black and Hispanic populations which, as in the other NIA population studies, will focus on functional status; risk factors; behavioral, social and environmental interplay; and health outcomes. The clinical trial on related systolic hypertension in the elderly, supported in collaboration with NHLBI, will enter patients into the definitive trial. In association with NINCDS, NIA will add cells from familial Alzheimer disease patients and their relatives to the NIA cell bank which will offer a unique opportunity to study the molecular and genetic changes in this disorder.

Support for research training and faculty development will be significantly expanded. Planned major new initiatives are to add aging-related research training to existing strong disease-oriented training programs, to provide mid-career reorientation for research and teaching in aging, to support leaders of aging-related activities in medical and other professional schools, and to encourage medical and other students (including minorities) to undertake research careers in aging. These expanded and new initiatives will produce approximately the number of trainees per year which is estimated to be necessary in order to reach the goals established for the years 1990 and 2000 in the DHHS Report on Education and Training in Geriatrics and Gerontology.

● Intramural Research

The NIA intramural program will expand existing programs and initiate substantial new research and training activities at its facilities in Baltimore and Bethesda. A research group on molecular genetics will be established to apply recombinant DNA and related techniques to the

study of aging. This new capability will significantly enhance many of the ongoing activities of the Laboratory of Cellular and Molecular Biology and other NIA intramural laboratories. In Bethesda, new neuropathological and neurochemical postmortem studies will supplement the present clinical investigation of Alzheimer disease and other dementias. The Baltimore Longitudinal Study of Aging will provide increased opportunity for cross-correlation among findings and for enhanced collaborative participation by scientists around the Nation. In collaboration with the Health Care Financing Administration, NIA will conduct research on behavioral interventions to control urinary and fecal incontinence in institutionalized elderly patients. Other areas of expanded clinical research will include immunology, metabolism, and cardiology.

- Research Management and Support

A student clerkship program will be implemented to bring medical students to the NIH during the summer months to acquaint them with the NIA and its programs and to encourage them to enter the field of aging.

II. Areas of Scientific Opportunity

- Manifestations of Aging

Our perceptions of the manifestations of aging are changing with the lengthening life span, particularly among those who are already old, and with changing patterns of morbidity and loss of function. Information on these changes is still limited and sketchy. Demographic and epidemiologic studies are in progress which emphasize the vulnerable, rapidly growing population over age 85 and explore trends in mortality, morbidity, disability, and everyday functioning. Opportunities for such studies are being pursued through the NIA in the following activities:

Established Populations for Epidemiologic Studies of the Elderly (EPESE) are in their fourth year in two urban (Boston and New Haven) areas and one rural (Iowa) area, through contractual arrangements. A total of 10,000 people over age 65 are being followed to determine patterns over time of health and diseases, functional status, risk factors, behavioral, social and environmental interplay, and health outcomes, as well as histories of health utilization and institutionalization. Black and Hispanic populations will be added to these in-depth studies.

National Health and Nutritional Examination Survey I (NHANES), Epidemiologic Follow-up Survey will enter its fifth year. The NIA serves as the lead agency in the seven-Institute collaboration. In addition to being the largest survey of nutritional states and subsequent health, it also provides extensive data on the relationship of specific diseases with detailed prior information on physical and mental health, occupation, health-related behavior, and numerous other variables.

Baltimore Longitudinal Study of the Aged (BLSA), now in its twenty-sixth year for males and sixth year for females, currently includes about 900 active participants. Serial observations include medical, genetic, biochemical, physiological, and behavioral variables. Each additional cycle of examinations enriches our knowledge base concerning normative aging. Reorganization of the management of the BLSA provides for increased opportunity for cross-correlation among findings and for appropriate collaborative participation by scientists around the Nation together with those in the Gerontology Research Center.

Among the significant results of the past year is the finding that in older persons who are free of any evidence of heart disease (including exclusion of even subtle degrees of coronary artery disease through use of radioactive thallium scanning) the maximum cardiac output in standardized stress tolerance testing is as great as that in normal young subjects; that is, in the normal human heart there is no decline in maximum functional capacity with age. There is a slower heart rate response to exercise stress (which appears to be related to lesser responsiveness to catecholamines), but the older heart adequately compensates through a larger stroke volume. Another recent significant series of studies demonstrates that personality characteristics remain remarkably stable throughout life into old age.

The Oldest Old Population over 85 years is the fastest growing segment of our population. There is little available information on this population in terms of those individuals with continuing good health and functioning as well as those with extensive degrees of disability. Given the high ratio of females to males in this age group, further research on sex differences in mortality and morbidity is important. Moreover there is a need to assess the rate of change in morbidity and disability among different cohorts of the elderly as well as to improve predictions of the growth of this age group. The Behavioral Sciences Research program is preparing a program announcement on the "oldest old."

Biological Markers of Aging, the above studies and others emphasize our need to obtain a better understanding of what is "normal" biological and psychological aging and what changes occurring with age are in reality due to diseases, occult as well as obvious, or due to other external environmental factors. We are currently developing contracts to support rodent colonies for use in the development of biological markers of aging. Of particular interest is the fact that these colonies will include dietary-restricted animals, which may be the ideal subject for aging studies since these animals attain the species maximum lifespan. We have also negotiated a contract to develop biomarkers of aging in primates. Such markers will be useful for evaluating segmental interventions in aging processes.

The numbers of persons aged 65 and older in our Nation will double in the next 35 years, from the present 26 million to over 52 million, and the proportions who are very old will be increasing at an even

greater rate. Our knowledge about very old persons is quite sparse. These studies will help to determine the effects of these shifts toward an increasing elderly population and will directly address the broad issues of normal aging, health, and quality of life, as well as help to define the necessary roles of individuals, families, communities, and costly health-related institutions and services.

● Application of New Techniques in Molecular Biology to Understand Aging

The opportunity exists to understand and potentially influence the genetically determined alterations and/or irreparable damage to the genome which may be ultimately responsible for senescence. Historically, the analysis of changes that occur in the genome of differentiated cells with time has been hampered by a lack of identifiable loci related to the senescent phenotype and by a lack of probes of sufficient specificity.

In the last few years, powerful new techniques have emerged in molecular biology. The procedures of molecular cloning and gene transfer have provided valuable information on the nature of carcinogenesis at the molecular level. It is now timely to apply this technology to examine the nature of aging at the molecular level.

- The first attempt to examine changes in gene structure with aging using gene probes was conducted by National Institute on Aging (NIA) grantees. They observed a loss of chromosomal alu and inter-alu sequences with in vitro as well as in vivo aging. More recent studies by these grantees have revealed that inter-alu genes accumulated extrachromosomally with aging. While these findings must be confirmed by other laboratories, they present intriguing views of the effect of aging on cellular DNA. NIA also supports fundamental studies on the nature of DNA transactions by one of the most talented groups in recombinant DNA research.
- In order to provide leadership in this field in our intramural program and to aid our established laboratories in extending their research capabilities through the use of these new techniques, it is proposed to establish a research group on molecular genetics and to recruit a molecular geneticist interested in applying recombinant DNA and related techniques in the study of aging. The introduction of recombinant DNA technology will significantly enhance many of the ongoing research activities of the Laboratory of Cellular and Molecular Biology and other intramural laboratories at the Gerontology Research Center. For example, DNA sequences susceptible to conversion to Z conformation could be incorporated into natural DNA molecules of various types, and the conformational flexibility and RNA synthesizing capability of the product studied. In the Clinical Physiology Branch, ongoing studies have documented decline in functional ability of the immune system with normal aging without loss of any morphologically identifiable cell populations. Therefore,

the genome's ability to program cell function must be disrupted and is an important focus for further research.

- We anticipate that molecular biologic techniques will be employed to examine other changes with aging in relation to gene function and structure, for example through utilizing a variety of cloned c-DNA probes for genes which can be identified to have functionally important alterations with aging, i.e., interleukin II, choline acetyltransferase. In addition, using restriction enzyme polymorphic patterns, it should be possible to localize the gene(s) responsible for the inherited form of Alzheimer disease. It might then be possible to isolate, transcribe, and then translate these sequences, which in turn could lead to the elucidation of molecular lesions involved in this devastating illness. Cells from affected and nonaffected individual members of a large family afflicted with familial Alzheimer disease are being added to the NIA Cell Bank in collaboration with NINCDS. The creation of this resource will facilitate this important molecular research.

An understanding of aging processes at a molecular level will permit the development of effective strategies for promoting maintenance of health and the prevention of age-related diseases. This can be most effectively accomplished by promoting the use of new recombinant DNA technology to gain insight into the molecular mechanisms of aging.

- Maintenance of Health and Effective Functioning in Middle and Later Life

Since the 20th century revolution in longevity does not mean inevitable decrepitude for most old people, there is a pressing need to discover how, why, and under what conditions age-related declines may be prevented, reversed or ameliorated. Recent research findings are suggesting how the productive middle years might be extended, how many disabilities of old age might be prevented or postponed, and how the costs of health care and dependency might be contained.

- Intellectual functioning, memory, perception, and psychomotor skills have been found to be both widely variable and extremely malleable. Contrary to conventional wisdom, few healthy individuals up to age 60, and less than half even at age 80, show reliable decrements in cognitive test performance as they grow older. Given training and incentives, elderly people can learn to perform as well on tests as people 20 years younger than they, and deficits in reaction time can often be remedied. New studies are seeking components of intellectual functioning, not currently measured in standard tests, that draw upon experience and may develop or improve in middle or later life. Further intensive study is needed of specific cognitive, perceptual, and neuropsychological processes as they affect older people's productivity and effective functioning in everyday living.

- Research on social and environmental interventions is identifying conditions and strategies for preventing, reversing, or alleviating many old age disabilities. For example, jobs can be modified to improve intellectual functioning, productivity, and health of older workers; special assistance from family and neighbors can be arranged to maintain independent functioning in the home; even in nursing homes, regimens can be established to restore activity, personal control, and well-being of elderly patients. Research is needed to specify how the social environments of older people can optimize health and functioning.
- Aspects of lifestyle, such as poor nutrition, lack of exercise, and cigarette smoking, are commanding research attention as they account for over half of U.S. deaths. The nutrition program aims to define the nutritional requirements for good health in the elderly; to determine how dietary deficiencies are associated with depressed immuno-competence, depressed cognitive function, or overt metabolic disease; and how eating behaviors change with aging. The exercise physiology program examines how physiologic (e.g., pulmonary, cardiovascular, or neuromuscular) adaptation to exercise is altered by aging, and whether regular long-term physical activity is associated with the prevention of age-related disorders (e.g., hypertension, maturity onset diabetes mellitus, and senile and postmenopausal osteoporosis).
- Behavioral geriatrics research, an emerging area of behavioral medicine, concerns health-related attitudes and behaviors of old people and health-care providers, including medical beliefs about the nature of the aging process, such "illness behaviors" as how older individuals monitor their bodily functioning and whether they take remedial action and comply with prescribed regimens, and the value of home visits in treating elderly patients. Research is needed on how health attitudes and behaviors are acquired, are affected by daily living, change as people grow older, and can be modified as scientific knowledge advances; and on how these behaviors and attitudes are linked with physiological and psychological aging processes to influence morbidity and mortality.

As longevity continues to increase and the absolute numbers of older people rise, the need for improved health and functioning will become overwhelming well before the end of the century. Thus it is essential to start now to provide the knowledge base for (a) reducing the 5 percent of those 65 and over who require institutional care, and (b) for optimizing the abilities of older people in general to function productively. Scholars are becoming aware of the relevance of aging to their disciplines through, e.g., the IOM reports on Health and Behavior and on Stress; and through the leadership by NIA in the NIH Working Group on Health and Behavior and in the PHS initiative in this area. Large data sets are archived for general use, and powerful models of measurement and analysis have been developed for use in field and laboratory trials and in longitudinal and cohort studies.

Now is the time to engage these scientific resources in the cause of sustaining vigorous health, well-being, productivity, and independence into the last years of life.

- Alzheimer Disease and Related Dementing Disorders of the Aged/Neuroscience of Aging

Although systematic studies of age-related changes in the human brain have a 100-year history, few investigators were interested in this subject until recently. During the last few years, a growing community of neuroscientists has begun to study a broad range of topics in the neurobiology of aging and dementing disorders of the aged. Only five years ago, very little was known about "senility." Senile dementia and Alzheimer disease were considered hopeless afflictions of the aged. Now we know that there are chemical and physical changes in the brain which can account for the memory deficits in Alzheimer disease and benign forgetfulness of the aged. The pace of scientific progress in this area of research has been truly remarkable. For the first time, it is possible to obtain a detailed picture of what happens at the molecular level of a neuron as well as a clearer idea of how large numbers of nerve cells cooperate in elaborating complex human behaviors such as learning and memory. Major opportunities for research on social and behavioral aspects of Alzheimer disease have been identified by the recent HHS task force on Families, Informal Support and SDAT. It is a crucial time to capitalize on the scientific momentum in the neuroscience of aging if we are to make progress in preventing and treating the dementing disorders of the aged.

- Genetic studies related to Alzheimer disease provide very exciting and unique opportunities, particularly because of the recent "bracketing" of a potential Huntington's disease gene. Procedures developed for the study of cell biology and membrane phenomena such as recombinant DNA and monoclonal antibody are proving to be very useful for the study of pathological processes in aging and Alzheimer disease.
- Recent findings have linked an infectious agent known as a prion to Alzheimer disease and several other degenerative disorders of the brain. More recent evidence suggests that prions and amyloid plaques may have structural and chemical similarities that are indistinguishable. If further studies prove that prions and amyloid are the same, these results will lead to a major breakthrough in understanding the etiology of not only Alzheimer disease, but other degenerative diseases as well.
- The finding that fetal brain tissue transplants can survive and function normally in older animals is an important discovery. When such procedures are perfected with further animal studies, they promise to be useful therapeutic tools. This form of treatment may enable us to restore lost neurochemical function in various parts of the brain.

- Early and accurate diagnosis of Alzheimer disease remains a serious impediment to the progress of research on this disease. Recently, NIA organized a research planning workshop to identify opportunities related to the diagnosis of Alzheimer disease. The proceedings of this workshop will be used by NIA to determine specific areas of research for special emphasis.
- Behavioral studies of basic cognitive processes in relation to aging provide unique opportunities for improving the sensitivity and specificity of diagnostic tests for memory disorders. Especially important areas of research include behavioral and social studies of the relation of availability and types of care to progress of the disease.
- Laboratory of Neurosciences (LNS) Intramural Program. A six-bed patient care unit and outpatient dementia clinic have been established in the Clinical Center-ACRF in Bethesda. The natural histories of Alzheimer disease and other dementias are evaluated with clinical test instruments, positron emission tomography (PET), and will be supplemented by neuropathological and neurochemical postmortem studies. The Laboratory of Neurosciences has already shown that in relation to age-matched control data, significant regional reductions in cerebral metabolism occur in early Alzheimer disease and can be related to specific cognitive defects. Furthermore, Down syndrome, which shows neuropathology characteristic of Alzheimer disease after 35 years, was shown to be accompanied by an elevated, abnormal cerebral metabolic rate in young adults. PET may be useful for the differential diagnosis of the dementias and for plotting the course and intensity of disease in relation to different therapies.
- There is a need for multicenter, longitudinal studies of the natural history of Alzheimer disease, its impact on families, and the value of the various approaches to treatment and sociobehavioral and environmental support.
- As an extension to the NIA and WHO initiatives in senile dementia, the NIA will sponsor, in cooperation with WHO and the European Economic Commission, a conference on the diagnosis of Alzheimer disease during the 1985 International Congress of Gerontology. This is expected to be the first in a series of efforts involving NIA, WHO and its member nations to standardize the nomenclature and diagnostic criteria of Alzheimer disease.

Among the many aging-related disabilities that require long-term care, those related to changes in brain functioning, particularly those that affect cognitive functioning, have significant implications for public policy related to health care services as well as national priorities for biomedical research. The social and economic burden of caring for cognitively impaired elderly is a growing concern which has attracted national attention both in Congress and the media. In the 1984 appropriation, the Congress provided funds to the

NIA for the establishment of specialized research centers on Alzheimer disease. Also the Secretary of Health and Human Services has established a special task force on Alzheimer disease. At present, the scientific community has the tools, the knowledge base and the means to attack the problems of Alzheimer disease. It is feasible to make a major breakthrough in this area of research in the foreseeable future provided there is a major national commitment, the appropriate resources are made available to the medical and scientific communities, and the commitment is sustained for a minimum of ten years.

- Extending the Research Base in Geriatrics

A number of disorders and diseases that afflict older people and result in disability and institutionalization have received too little research attention from the medical community. These include the major types of functional disabilities; namely, the dementias like Alzheimer disease (the topic of a separate special opportunity statement), urinary incontinence, and problems of mobility with the frequently associated complications of falls and hip fractures. These conditions and certain of the common diseases of old age are being addressed through extramural support for clinical research in geriatrics and through intramural efforts; many of the activities are being conducted in collaboration with other institutes and academic institutions. Specific examples follow:

- Urinary Incontinence in the Elderly. This disorder may affect as much as 10% of our older population and significantly restrict activities in as many as 500,000 older Americans. Over the past three years, the NIA has conducted several developmental activities in the area of urinary incontinence including very promising intramural research on the use of behavioral interventions, two research workshops, and a program announcement. Preliminary results from both the intramural research and the work of others suggest that behavioral therapies and biofeedback for urinary incontinence may be highly efficacious in older persons. In collaboration with the Division of Nursing, Health Resources and Services Administration, we have issued a Request for Applications for cooperative agreements to support clinical trials of behavioral therapies for urinary incontinence. Our intramural program is completing negotiations with the Health Care Financing Administration and the Office of the Surgeon General to extend their research on behavioral interventions to institutionalized elderly patients with urinary and fecal incontinence. In addition, an initiative is being organized to study the pathophysiology of detrusor dysfunction, a major cause of urinary incontinence.
- Falls. Falling is a very common and hazardous problem for older people; studies have shown that up to 50% of those over the age of 75 fall once or more per year; there is greatly increased morbidity and mortality among those who fall, including the

devastating and expensive problem of hip fracture. Falls in older persons are associated with a number of risk factors including gait and balance disorders, neuromuscular dysfunction, impaired vision and hearing, impaired mental function, and the side effects of drugs. Environmental hazards also frequently contribute but are rarely the sole cause. Some research on falls is already under way through support from the Teaching Nursing Home grants. To stimulate better understanding and more interest in research in this area, a research workshop is planned to be followed by a Request for Applications for research on the important contributing factors. It may also be noted that the NIA has taken a leading role in a special workgroup set up by the Surgeon General in collaboration with several other Federal agencies to develop a plan for efforts to educate the public about the risks of falls and preventive steps which should be taken.

- Increased Susceptibility to Infectious Diseases. In collaboration with NIAID, a research workshop has been held which considered all aspects of this problem in older people. The workshop results have been published and a program announcement has been issued to promote increased research related to epidemiology, etiology, prevention, diagnosis, and treatment of infectious diseases in older persons. An initiative is also being developed to support research on the relationships between the decline in certain immune functions with aging and the increased susceptibility of older individuals to infections.
- Systolic Hypertension in the Elderly. In collaboration with NHLBI, the NIA is supporting a clinical trial on isolated systolic hypertension in the elderly. One end point will be multiple cerebral infarcts, a major cause of senile dementia. This clinical trial will also afford the opportunity to examine other questions, such as the possible effect of the drug chlorthalidone (the diuretic which is to be used in the clinical trial) on the rate of bone loss in older persons. Thiazide diuretics have been reported to delay bone loss and thus the thiazide-like agent chlorthalidone might be useful in the prevention of osteoporosis.
- Osteoporosis and Osteoarthritis. NIA is collaborating with the NIADDK and the Office of Medical Applications of Research in the sponsorship of a consensus development conference on the treatment of osteoporosis, a very common problem particularly in older white women and a major contributing factor in hip fracture and general loss of mobility. In relation to the very common problem of osteoarthritis in older age, NIA is working with NIADDK to extend the research efforts of both institutes.

In the past two years, the Johns Hopkins Medical Institutions have taken major steps to increase their commitment to research and training related to geriatric medicine. These include the appointment of a Deputy Chairman of the Department of Medicine

and Director of Geriatric Medicine, the completion of negotiations for Johns Hopkins to acquire ownership of and operate the Baltimore City Hospitals (the site of the Gerontology Research Center (GRC) of NIA), successful competition by Johns Hopkins for a Teaching Nursing Home grant, and expressions of major interest on its part in expanding clinical research in geriatrics, particularly in the Baltimore City Hospitals in collaboration with the GRC. The GRC and Johns Hopkins have undertaken a shared responsibility for a three-year research fellowship program aimed at producing highly qualified investigators and academic leaders in this field. Areas of expanded clinical research which are promising at this time, in light of the staff capabilities already present in the GRC, include clinical immunology, metabolism, and cardiology.

- Teaching Nursing Home (TNH) Program. Following its inception in 1982, this program has already begun to show results, in the form of both significant research advances and an increased emphasis on clinical aging research at major medical centers. Important findings reported by TNH awardees include beneficial effects of the drug physostigmine in some patients with Alzheimer disease, and detection of aging changes in the lower urinary tract that predispose to infections. The six TNH awardees are also attracting proposals from other researchers at their institutions to develop clinical aging research projects in a variety of fields, using subject populations and data bases developed by the awardees. In addition, other institutions with a commitment to clinical aging research are developing TNH proposals.

Maintaining effective functioning and independence in living for older people, to the maximum extent possible, in the face of chronic diseases and disabilities, is the primary aim of geriatrics. The extent to which we can improve our capabilities to address such problems successfully will determine to a large degree what the burden of care is going to be, for individuals, families and society, as our numbers of old and very old people rapidly increase.

- Strengthened Training and Research Career Development in Gerontology and Geriatrics

A major challenge continues to face us to meet the needs for training in two major, interrelated approaches to aging and the problems of older people: 1) training investigators to pursue the enlarging research opportunities, and 2) preparing faculties to teach these topics to present and future health professionals.

A broad consensus has developed in medical and other health professional schools about the need to strengthen and extend their capacities and activities with respect to programs in aging. This has been documented in such reports as that of the Institute of Medicine, NAS, on "Aging and Medical Education" (1978) and the summary report of the Association of American Medical Colleges on its nationwide series of

Institutes on Geriatrics and Medical Education (1982), as well as position statements of many other professional bodies. A major study by staff of the Rand Corporation and UCLA in 1981 concluded that at least 1350 physician faculty members are needed to meet the responsibilities of the Nation's medical schools for teaching in this field, and an additional 1350 to 2000 research personnel are required to establish a sound nucleus of scientific investigation focused on issues of aging and the aged (in addition to the expectation that many physician faculty members will also be involved in research). From various sources our current estimates are that we have no more than 10 percent of the needed personnel for teaching and research in these fields.

The present rate of training for research and teaching related to aging--in basic biomedical, behavioral and social, and clinically related fields--amounts to about 100-120 new persons per year. This figure includes intramurally and extramurally supported training by the NIA and specifically aging-related training by other Institutes of NIH, NIMH, the VA, AoA, and private foundations. In the past, a limitation has been the numbers of persons eager to enter this field. This, however, is changing with many more able candidates available for training positions and rapidly increasing interests among medical and other students. In addition, scientists and teachers in mid-career in other fields are expressing an interest in reorienting themselves into aging-related work. Medical and other professional schools are trying, for the most part unsuccessfully at present because of the lack of qualified manpower, to recruit new faculty into these fields.

The public's awareness of and concern about these needs are expressed in many ways, of which perhaps the most relevant is the directive of the House Committee on Appropriations in its report on the FY 1984 budget, that the Department (including the NIA, NIMH, HRSA, and AoA) develop a plan to improve and expand training in geriatrics and gerontology. This report is to include training for research as well as training for care of older people. There is a general consensus that essentially all health professionals should be adequately prepared with knowledge and skills in aging and the strength and problems of older people.

In response to these needs and directives, the NIA is providing leadership to the Committee representing the four DHHS agencies (plus the VA and DoD) which is completing a preliminary estimate of needs, a summary of the current status of accomplishments to meet these needs, and a plan for further steps. Overall, it seems clear that our efforts to train the needed investigators and teachers should be at least doubled at this time and further increased in the next five to six years if we are to approach fulfillment of the needs in this field by the year 2000. In addition to expanding the use of existing mechanisms for support of research training and faculty development for scientists in biomedical, behavioral, and social disciplines as they relate to aging, several new approaches are proposed:

- fellowship support for adding aging-related research training to existing strong disease-oriented training programs, in settings where such additions would be well received and well directed;
- support for mid-career reorientation for research and teaching in aging through mechanisms such as senior fellowships;
- support for leaders of aging-related activities in medical and other professional schools, analagous to the support in the past by the NCI of cancer coordinators and by NHLBI of coordinators of teaching related to heart disease; and
- additional incentives to encourage medical and other students (including minorities) to undertake research careers in aging.

As noted above, there is a general consensus in the public and in the health professions that, to meet the needs of our rapidly growing aging population, virtually all health professionals and allied workers require knowledge and skills with respect to aging and the strengths and problems of older people. However, today relatively few have had the opportunity to enhance their capacities in these fields. In addition, the development of research opportunities requires many more well-prepared investigators in the biomedical, behavioral, and clinical aspects of aging.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

I. Major Program Changes, FY 1986

The FY 1986 Budget Request would permit NIAID to expand important elements of its ongoing programs.

A number of major clinical trials would be initiated to fully capitalize on significant advances flowing from the Institute's more basic and applied research efforts. The Microbiology and Infectious Diseases Program would support the conduct of trials on an attenuated, live influenza vaccine; a vaccine for rotavirus diarrhea; rimantadine as a treatment for influenza in patients with chronic obstructive pulmonary disease; ribavirin therapy of viral respiratory diseases; and vaccines for group B streptococcal infections. The Immunology, Allergic and Immunologic Diseases Program would fund trials in the immunotherapy of laboratory animal allergy; the use of monoclonal antibodies in bone marrow transplants; and the use of monoclonal antibodies in kidney transplants. Intramural scientists would conduct trials on the prophylaxis of anaphylactoid reactions and on the use of gamma globulin in the treatment of AIDS.

The Institute views its Accelerated Development of New Vaccines Program as an important opportunity to reduce the medical and financial impact of ten diseases on the nation. The Institute of Medicine is developing a method for establishing priorities among the various candidate vaccines based on scientific, economic and other parameters. This Budget Request will permit the optimal support of the full array of basic, applied, and developmental studies needed to accelerate those vaccines of highest priority.

This Budget Request will permit NIAID to pursue several important investigations on the Acquired Immune Deficiency Syndrome. Included are studies on reconstitution of the immune system of AIDS patients, treatment of the primary virus infection that causes AIDS, prevention of AIDS virus infections in high risk individuals through the use of antiviral chemoprophylaxis, research on a vaccine to prevent the disease, and research on how the viral infection destroys the immune system.

II. Areas of Scientific Opportunity

● The Immune System and Its Diseases

The recognition of the "Immune System" as an anatomic and physiologic entity is a relatively recent event. Early studies in immunology focused predominantly on the functional aspects of the immune response through the manipulation of humoral or cellular responses. Recently the application of sophisticated modern techniques of immunochemistry, cell biology, and molecular biology has revealed the immune system to

be a complex network of specialized organs, cells, and regulatory chemical substances. The impact of the science of immunology on virtually every field of medicine is widely acknowledged. It relates to the etiology, diagnosis, prevention, or treatment of a multitude of diseases. Further gains will depend on developing an increased understanding of the immune system as an organ system. Because of the complexity of the immune system, it is obvious that there are numerous possibilities for disturbances in function. There is an ongoing list of inherited congenital and acquired immunological diseases that occur because of deficiencies or abnormalities in regulation.

With recent insights into their underlying mechanisms, many diseases that long mystified physicians are now known to relate to responses of the immune system. Some conditions, such as several immune deficiency diseases and such autoimmune disorders as systemic lupus erythematosus, are almost exclusively problems or altered states of the immune system. Many other ailments including asthma, other allergies, drug reactions, chronic infections, juvenile diabetes, multiple sclerosis, and malignancies (especially the lymphomas and leukemias) have important immunologic components. As investigators continue to explore the intricate workings of the immune system, other diseases will undoubtedly be discovered to have immunologic origins. It is the understanding of the system and its mechanisms of action and regulation that has led to these clinical findings. Revolutionary new techniques have put us on the brink of attaining new insights into the workings of the immune system and within reach of significant payoffs.

The immune system is able to mount a specific response to an almost infinite number of foreign substances. This remarkable feat is accomplished in several ways. First it stockpiles a tremendous arsenal of immune-competent cells. By storing just a few cells specific for each potentially encountered antigen, it has ample room for a broad range of specificities. When a foreign substance becomes manifest, a few specific cells are stimulated to multiply into a full-scale population of effector cells through powerful proliferative mechanisms. In order that this reaction will not wildly over-expand like a cancer, equally powerful regulatory mechanisms check the proliferation. An organism must also refrain from attacking its own antigens and this requirement has led to the development in the immune system of several levels of control which prevent or minimize the appearance of self-immune attack or autoimmunity.

The immune system can be viewed as consisting of two distinct arms: one, functioning primarily through the action of certain types of cells, is referred to as cell-mediated; the other, functioning through antibodies, is referred to as humoral. However, both arms rely on white blood cells of the lymphocytic/monocytic series.

Cell-mediated immunity involves primarily T lymphocytes or T cells which are processed by the thymus. T cells can attack an antigen directly but they also produce a variety of chemical substances

(lymphokines) that attract or activate other parts of the immune system. Cell-mediated immunity is a major factor in the rejection of transplanted organs and appears important in protecting the body against cancer.

Humoral immunity involves B lymphocytes or B cells, which are derived from the bone marrow and produce antibody forming cells. When B cells react with an antigen, they divide and become capable of producing large numbers of antibodies. These antibodies have the same specificity as the B cells that produce them; that is, they recognize the same antigen.

Recently, scientists have discovered that T cells may either help (inducer-helper T cells) or suppress (suppressor T cells) B cells activated to produce antibodies. This collaboration has proved to be a key factor in manipulating certain segments of the immune response.

A principal point in understanding regulation of the immune response is the concept that these regulatory interactions are complex, involving many cells which may be organized into "circuits." Once we fully understand how the various cells and organs of the immune system communicate with each other we will understand better how the system is regulated. A full understanding of immunoregulation will make possible the clinical manipulation of the system to correct defects and treat disease states.

- Accelerated Development of New Vaccines

The purpose of this program is to develop a clearly identified, widely recognized, and well coordinated approach to the further conquest of vaccine preventable diseases. The new knowledge and technologies which have been emerging from basic research in recombinant DNA and hybridoma technologies and in the better understanding of the workings of the immune system now provide opportunities to solve problems that have been insolvable with earlier technology and knowledge. Such new knowledge will permit radically different approaches to some of the current problems of immunization. The goal of the program is to expedite the availability of needed vaccines through the selection of a few candidate vaccines for intense and expanded effort so as to bring these vaccines into use several years earlier than might otherwise have been the case. This NIAID program contains projects directed at all necessary aspects of vaccine development from some fundamental studies on the etiologic agents through identification of the immunogenic antigens to developmental studies on vaccine production.

An expanded initiative on development and subsequent use of new and improved vaccines supports the DHHS policy to emphasize the prevention of disease. As measles, poliomyelitis, diphtheria, and pertussis vaccines have so clearly shown, immunization offers the most cost effective means of control of infectious diseases. With new technology promising to provide the capability to solve problems that have prevented progress in the past, a definite program to exploit this

opportunity was established. Industry is making large investments in recombinant DNA and hybridoma technologies, some of which are directed at vaccines, and establishment of a definitive federal program on new vaccines should further encourage such efforts on the part of industry.

Infectious diseases constitute major problems for U.S. health authorities and citizens because of high morbidity, medical costs, interference with education and productivity, and crippling complications. Some significant statistics are:

- In 1981 there were 251 million acute respiratory illnesses in the United States, resulting in 476 million days in bed, 141 million days lost from work and 98 million days lost from school.
- Acute gastroenteritis is the second most common illness, accounting in one survey for 9.5 percent of all visits to pediatricians' offices.
- Infectious diseases result in approximately 27 million patient days of acute hospital care each year (10 percent of the patient days in acute care hospitals) at an estimated direct cost of nearly \$6 billion.
- Infectious diseases continue to be more prevalent in poverty areas and areas with high immigration rates. Up to 80 percent of screened refugees had at least one intestinal parasite; 55 percent, more than one. Malaria, hepatitis and diarrheal diseases of viral, bacterial or parasitic origin, remain serious health hazards of international travel.
- In 1980 there were seven million new or recurrent episodes of genital herpes, three million chlamydial infections, three million trichomoniasis cases, two million gonorrhea cases, and 100,000 cases of syphilis. These led to one million cases of pelvic inflammatory disease, 300,000 damaged infants, 200,000 infertile women, and \$2.5 billion in direct and indirect costs.

Although the number of effective antibiotics, antivirals, and anti-parasitic drugs available for the treatment of many of these infections is growing, prevention is preferable; that is the objective of the Accelerated Development of New Vaccines Program which currently is developing vaccines for the following diseases:

Meningitis	Diarrhea
"Hemophilus influenzae"	Cholera
Group B Streptococci	Dysentery
	Rotaviruses
	Typhoid
Gonorrhea	
	Hepatitis
Bronchiolitis, croup, and	Type A
pneumonia in children	Type B (2nd generation)
Parainfluenza viruses	
Respiratory syncytial viruses	Chickenpox
Whooping cough	Genital Herpes
Influenza	Malaria

● Acquired Immune Deficiency Syndrome

This devastating disease has continued to increase in epidemic proportions. Few diseases in the recent past have caused as much public and congressional interest in research on its etiology, epidemiology, and treatment. Scientific interest is also fully developed and many lines of investigation are being actively pursued. Because of its mission to support research in immunology and infectious diseases, the NIAID is centrally situated in the investigation.

In May 1984, approximately two and one-half years after the first published description, the total number of cases diagnosed in the United States exceeded 4000 and more than 1700 of the patients had succumbed. The CDC were receiving reports of several new cases per day.

NIAID is supporting and conducting major projects to: study the etiologic agent; define the epidemiology and natural history of the disease; establish a repository for tissues and fluids as a research resource; develop methods for early detection of disease; study the immunologic abnormalities of the disease; conduct therapeutic trials with agents to attempt to reconstitute the immune system; study the opportunistic infections which kill AIDS patients; and develop treatment for these opportunistic infections.

In addition to the research cited above which is directly related to AIDS the Institute has a considerable amount of work that is indirectly related. The indirectly related work encompasses cellular immunity as a general phenomenon, interferon, key viruses, and sexually transmitted disease research.

● Virology

The study of viruses has had and continues to exert a large impact on a wide range of scientific and medical problems. The history of virus research mirrors the progression, found in most disciplines, going from descriptive approaches, rooted in bacteriology as well as in human, animal, and plant pathology, to the era of molecular biology

that has come to dominate all branches of biomedical science. The fact that viruses, as bearers of unique genetic information encoded in their DNA or RNA, bring into cells conveniently small probes of essential life processes has made them the cornerstone of molecular biology. Their structural diversity has contributed greatly to an understanding of macromolecular organization and assembly.

Each virus is capable of interacting, in very specific ways, with different kinds of cells. This interaction may span the entire range from a highly virulent interaction, with the virus usurping the cell's synthetic machinery and killing the cell, to a temperate interchange, with the viral genome becoming an integrated part of the cell's chromosomal apparatus. In all cases--and there are many intermediate permutations of these two extremes--the expression of viral gene functions imposes a variety of altered identities on infected cells. The detailed characterization of each possible specific outcome of a virus-cell interaction, extrapolated to the complex workings of the multicellular and differentiated higher organism, holds the key to the major goals of research in virology, i.e., an understanding of virus-induced diseases and development of means for their prevention and treatment through genetically engineered reassortant or hybrid viruses for use as live attenuated vaccines, through synthetic peptide vaccines or through specifically designed antiviral drugs.

Acute infections, as a group, are the largest current cause of illness in the U.S. The vast majority of such acute illness is the consequence of infection known or presumed to be caused by viruses. Ranging from relatively trivial to life-threatening, these illnesses exact direct and indirect costs amounting to many billions of dollars annually plus the immeasurable grief and discomfort suffered by those afflicted. Research on specific viral diseases (e.g. polio, measles, rubella) has yielded results in the form of effective vaccines that, measured only by the two billion dollars in direct costs saved each year, have returned many fold the costs of the related research. These successes clearly testify to the economic and social value of continued virologic research.

In the past, persistent viral infections have received significantly less attention than other areas of virology. Interest in persistent infections, however, has greatly increased in recent years as their great frequency and medical importance have become apparent. Recent findings have established the viral etiologies of several chronic diseases such as subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, kuru, and Creutzfeldt-Jakob disease. The fact that these diseases are caused by persistent viral infections suggests that other chronic diseases of unknown etiology in man and animals may be caused by persistent infection with known or as yet unrecognized viruses. It is thus likely that the full scope of persistent viral infections of medical and economic importance to man is not recognized today.

A further understanding of the basic mechanisms by which viruses persist in a host and escape elimination, as well as knowledge of the mechanisms of disease associated with persistent and recurrent infections, is necessary before practical advances toward control and rational treatment of the associated diseases can be expected.

Viruses provide ideal model systems for uncovering the fundamental principles underlying the molecular organization, genetics, and biological activities of cells and, ultimately, multicellular organisms, including humans. Virology, as a discipline, has progressed to the stage where it can be applied to in-depth investigation of the molecular events that determine cellular processes as they relate to health and disease.

NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE
AND KIDNEY DISEASES

I. Major Program Changes, FY 1986

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is responsible for research on a broad spectrum of diseases that are among the most common, chronic, disabling, and costly facing this nation. To conquer these diseases, the Institute maintains a strong fundamental and clinical research program in which innovative techniques in molecular biology, immunology, genetics, and other basic science disciplines are being applied to questions about the cause and progression of chronic diseases. Approximately 70 percent of the Institute's resources is devoted to investigator-initiated research project grants, through which scientists in the field identify the most promising research opportunities to pursue. Most of these studies are oriented toward fundamental research, which is essential to understanding the intrinsic nature of disease and is the basis for developing appropriate, effective strategies for prevention and therapy.

● Arthritis, Musculoskeletal, and Skin Diseases

The Arthritis Program plans to encourage additional high-quality research on the etiology of arthritis, including studies of possible infectious, genetic, and immunologic factors. For example, new research grant applications are expected to explore the recently reported isolation of a virus from the joint linings of rheumatoid arthritis patients. The virus, known as the RA-1 virus and believed to be a parvovirus, may be the cause of or simply associated with the inflammation and thickening of the synovial tissues in joints of affected individuals. Further research is thus needed to determine the role of this virus in the disease process. Research will also be encouraged on the possible relationship of mycoplasmas and rheumatoid arthritis, with studies to be undertaken along lines recommended by the National Arthritis Advisory Board. First, efforts will be made to identify rheumatoid arthritis patients who have evidence of mycoplasmas in their tissues. If a sufficient number of mycoplasma-positive patients are found, clinical studies of antibiotic therapy will be initiated. In osteoarthritis, a new clinical trial will attempt to determine the efficacy of cartilage transplantation to replace tissue destroyed by this disease. Osteoarthritis is the most common form of arthritis and the most prevalent motion-limiting disorder. It is not understood why damaged cartilage does not repair itself in this disease; however, biotechnological advances in transplantation of cartilage are sufficiently promising to warrant a clinical trial in this area. In addition, a conference on osteoarthritis is planned for the summer of 1985 and it is expected to generate new research ideas.

Guided by an extensive evaluation of research supported by the Musculoskeletal Diseases Program, two clinical trials are planned in this field. The first will explore the effectiveness of diphosphonate treatment for Paget's disease. This is a chronic condition characterized by abnormally rapid bone turnover resulting in dense but fragile bone, which most frequently occurs between the ages of 50 and 70. Although diphosphonates are known to be effective in treating Paget's disease, the form currently available in the United States can be taken for no longer than six months due to potential adverse side effects. Initial reports from Europe indicate improved efficacy of diphosphonates developed there; however, clinical studies are needed to confirm these reports by comparing the diphosphonates from Europe with those available in the United States. A second clinical trial in the Musculoskeletal Diseases Program will focus on low back pain, a difficult diagnostic and treatment problem and a persistent cause of pain and economic loss for millions of Americans. Low back pain is the most common cause of disability in young adults (between the ages of 17 and 44 years) in the United States. Building upon a recent NIADDK conference on low back pain, a carefully designed and executed clinical trial is planned on the efficacy and hazards of rest or exercise in the management of this condition. In addition, the Institute expects to support increased investigator-initiated research in osteoporosis, stimulated through a 1984 NIH Consensus Development Conference. Osteoporosis is characterized by decreased bone mass, and is a major cause of bone fractures in postmenopausal women in particular, and older persons in general.

The Skin Diseases Program plans to intensify research on epidermolysis bullosa (EB), a genetic disease characterized by abnormalities in the skin and mucous membranes resulting frequently in deformities of the hands and feet, malnutrition, and premature death. In many cases, victims suffer blisters which resemble a severe burn. The Institute plans to capitalize on the recent discovery that "anchoring fibrils," a previously unknown constituent of skin tissue, are either missing or deficient in patients with severe EB and may account for the devastating skin blistering experienced in this disease.

Multidisciplinary research will be encouraged with the goal of using EB as a model for applying new immunologic techniques to gain a better understanding of biological processes. Other components of the NIH, including NICHD, NIDR, NEI, NCI, and NIGMS, are expected to participate in this EB initiative. A clinical trial is also planned on the use of 13-cis retinoic acid in patients with acne vulgaris. Retinoids, which are vitamin A derivatives, have been demonstrated to be beneficial in studies of severe fulminant cystic acne vulgaris refractory to other treatment modalities. The new trial will attempt to determine if retinoids are useful in less severe forms of the disease and to gain a better understanding of side effects that may be associated with this experimental therapy.

● Diabetes, Endocrinology, and Metabolic Diseases

Increased investigator-initiated research is anticipated on genetic and immunologic factors in diabetes, as scientists continue to exploit many research opportunities which have developed during the past decade. For example, efforts will be directed toward identifying the "diabetes gene", now known to be located on chromosome 6; to determine how it causes destruction of insulin-producing beta cells; and to develop specific interventions. In addition, support will also be provided to extend basic and clinical studies related to autoimmunity in the etiology and pathogenesis of insulin dependent diabetes and to expand research on pancreatic islet transplantation as a potential therapeutic approach to the management and cure of this disease.

The diabetes Control and Complications Trial is expected to become fully operational in FY 1986, if the results of preliminary phases indicate that the trial is both feasible and advisable. In the full scale trial, the Institute would be studying more than 1,000 insulin-dependent diabetics over several years to determine whether near-normalization of blood glucose can prevent or ameliorate the early vascular complications of this disease.

The Diabetes Program also plans to stimulate additional studies to capitalize on research opportunities identified at the second National Conference on Diabetes, sponsored by the National Diabetes Advisory Board in conjunction with various Federal agencies and private organizations. During this conference, over 150 experts addressed promising avenues of research in the etiology of diabetes; insulin secretion, biosynthesis, and gene studies; hormone action; transplantation; insulin delivery systems; pregnancy; and the eye, kidney, neurologic, and cardiovascular complications of diabetes. The proceedings of the conference will serve to guide diabetes research efforts for the next several years.

The Endocrinology Program plans to intensify research on autoimmunity related to endocrine diseases, particularly as it is involved in thyroid disease, hypoparathyroidism, and hypoadrenalism. Additional investigator-initiated research in this area is expected as a result of solicitations for research grant applications in areas related to the physiology and pathophysiology of endocrine systems. Basic and clinical research will be expanded on the structure, biosynthesis, function, and mechanism of action of various hormones, on hormone control mechanisms, on the effects of these hormones on various metabolic processes, and on genes and other factors that relate to or modify endocrine effects. Specific studies will focus on thyroid, parathyroid, adrenal, pituitary, thymus, and pineal hormones, as well as on neuropeptides and prostaglandins. New techniques in molecular and cell biology will be applied to the production of hormones, hormone analogs, and other research resources which are fundamental to continued progress in basic and clinical research on endocrinology and various endocrine disorders.

A major aim of the Metabolic Diseases Program is to increase research on inherited metabolic diseases such as cystic fibrosis (CF), a disease in which the mucus-producing glands secrete a thick, sticky mucus. This abnormal mucus accumulates in various parts of the body and interferes with vital functions, such as breathing and digestion. Investigators will continue to search for the basic defect underlying this disease; to seek thus-far elusive procedures for detecting asymptomatic carriers of the disease; and to develop prenatal test for CF.

Increased support will also be provided for investigator-initiated research into enzymatic mechanisms and their regulation, biological transport, and membrane structure as they relate to the etiology, pathogenesis, diagnosis, treatment, and cure of acquired or inborn errors of metabolism. The latter represent a particularly important subgroup of genetic disorders in which the abnormality in the DNA of the gene is expressed by the production of an enzyme with abnormal activity. Despite their relatively low incidence, many of these "orphan diseases" have a clinical and research impact which is often far out of proportion to their numbers. The diseases that result from acquired or inborn errors of metabolism are based in every organ system, which gives them significance for every medical specialty and subspecialty. Continued research progress in this area will therefore reflect advances in various related areas of the basic biomedical sciences including both cellular and molecular biology.

- Digestive Diseases and Nutrition

The Digestive Diseases Program will pursue studies of underlying disease processes through the application of sophisticated new approaches in molecular biology, genetics, immunology, physical chemistry, investigative pharmacology, cell culture techniques, and diagnostic and surgical procedures. For example, the finding that viral DNA sequences can be integrated into host liver-cell DNA is providing a clue as to how chronic liver disease, particularly chronic active hepatitis, may progress to liver cancer. The development of a mixed collagen matrix has enabled researchers to establish colonies of liver cells that are viable for four to six months and has thus facilitated the study of specialized receptors on liver cells, transport processes, and bile secretion. Radioimmunoassay and monoclonal antibodies are making possible advanced studies of peptide hormones--including their sites of formation, receptors, metabolism, and function in the digestive tract and in the brain. Important opportunities exist to study the implications of the existence of these hormones in both the digestive and central nervous systems. In addition, recent advances in imaging, endoscopy, and function testing have made possible earlier and more accurate diagnosis of digestive diseases and provided opportunities for studying the etiology and natural history of digestive diseases in organs such as the pancreas, or the biliary tract, where study had previously been very difficult. An integrated approach is now needed to maximize available biotechnology, and also to exploit advancing technology in psychology,

statistics, decision analysis, and the use of computers to address clinical problems.

Initiatives on the causes and treatment of potentially fatal liver diseases that may ultimately require a liver transplantation will be pursued; a recent request for applications was issued by NIADDK in conjunction with several other NIH institutes. Studies on liver transplantation will be encouraged, addressing such topics as technical aspects of the liver transplantation procedure; methods to improve liver transplant survival such as use of monoclonal antibodies; immunological factors in liver rejection; the pharmacology of immunosuppressant drugs; and the genetic determinants of immunosuppressant drug metabolism. Investigators with interest and expertise in the area of organ preservation and evaluation of the donor organ are also being urged to submit research grant applications. Some avenues to be explored include pulsative perfusion of donor liver (used successfully in renal grafts); improved cold storage solutions; pharmacologic stabilization of the organ; improved assessment of the viability of the liver and the extent to which exposure to either hypoxia or hypotension has altered the function of the donor liver; and techniques to assess the degree of damage in a potential donor liver to determine when it is still compatible with recovery of normal liver function and successful transplantation. To help with these problems, the Institute is developing a liver transplantation research data base. It is identifying the key data necessary, operating definitions, methods of analysis, and a computer program to collect emerging research data on patients in the United States who have been evaluated and have had liver transplantation for a variety of end-stage liver diseases.

To stimulate multidisciplinary basic and clinical research and research training on digestive diseases, NIADDK will also be supporting a new program of research centers in this field. In addition, three new clinical trials in digestive diseases are planned in FY 1986. These trials will explore: (1) steroids in the treatment of acute, rapidly progressing liver disease; (2) injection of clotting solutions into dilated esophageal veins to control bleeding (sclerotherapy) in severe cirrhosis of the liver; and (3) therapy to prevent rejection in liver transplantation.

The Nutrition Program plans to initiate a clinical trial of perioperative nutritional support as a possible means of reducing operative morbidity or mortality in malnourished patients. This study will attempt to quantitate the effectiveness of total parenteral nutrition prior to and after surgery, since malnutrition is a severe concomitant condition in many patients with digestive diseases.

- Kidney, Urologic, and Hematologic Diseases

The Kidney Program will encourage expanded research on immune mechanisms in human kidney diseases, consistent with a recently published program announcement soliciting studies in this area. Particular

emphasis will be given to studies of glomerulonephritis (GN), a group of kidney diseases which involve immune abnormalities and which are implicated as a cause of one-third to one-half of the cases of end-stage renal disease in this country. Research will be encouraged in several areas, including investigation of genetic and immunologic host factors that predispose to the development of immune complex glomerulonephritis and other forms of antibody-mediated injury; studies to define the role of cell-mediated immunity in the pathogenesis of GN; and development of animal models in which cell-mediated injury is demonstrable. Investigators will also focus on the role of lymphoid cells, which may directly produce renal injury or which by immunoregulatory imbalance may cause disordered humoral immune responses; development of new markers and new ways of assessing functional activity of cells within infiltrates; and purported nonimmunologic mechanisms that may influence immunologically-initiated renal diseases. Many researchers are expected to capitalize on the development and refinement of monoclonal antibody techniques, which hold great promise for kidney research, as noted during a recent Institute-supported conference in this field.

The Kidney Program also expects to intensify research on the effect of dietary modification on the rate of progression of chronic renal disease, as a multi-center clinical trial in this area proceeds from the planning to the operational stage. A clinical trial is also planned to test the effects of intensive pulse therapy with corticosteroids, together with the immunosuppressant drug, cyclophosphamide, administered intermittently for several months to patients with membranoproliferative glomerulonephritis. A major goal of this trial is to increase efficacy of treatment and minimize drug-related side effects.

The Urologic Diseases Program will attempt to increase research efforts in benign prostatic hyperplasia disorders due to abnormal structure and function of the lower urinary tract and urinary tract infections, and to exploit recent research advances in the treatment of kidney and urinary tract stones. The Hematology Program will intensify research on the role of defective genes and abnormalities of gene expression in various anemias such as sickle cell anemia and thalassemia. Efforts will also be made to expand research on porphyria, a disease resulting from the deficiency of a specific enzyme in the synthetic pathway of heme, the nonprotein, pigment-containing part of the hemoglobin molecule. Acute attacks of porphyria can progress to coma, respiratory insufficiency, and death. Timely administration of the orphan drug hematin can reduce the severity of acute attacks of porphyria and may even prevent occurrence of the disease. Studies are now needed to determine an optimal treatment regimen for administration of hematin to establish criteria for drug formulation, and to assess side effects.

● Division of Intramural Research

The Intramural Research Program plans to intensify basic research by applying the most advanced techniques of biochemistry and cellular and molecular biology to fundamental studies of normal function and disease states. Emphasis will be given to the expanded use of modified techniques of molecular biology, including recombinant DNA technology, in studies of basic processes of cell regulation and differentiation. One of the practical applications of this technology to be pursued is the production of hormones and enzymes essential for replacement therapy in inherited metabolic diseases caused by absent or defective enzymes. Intramural research will also focus on improving the management of arthritis and other rheumatic diseases, diabetes, and digestive and kidney diseases. Scientists will vigorously pursue multidisciplinary approaches to diseases such as cystic fibrosis. A number of investigators with proven expertise in cell biology, infectious diseases, genetics, glycoproteins, and endocrinology are being encouraged to bring their collective expertise to bear on this disease. They will examine the genetics of inherited metabolic diseases, secretory processes and ion transport, and microorganisms that chronically infect the lungs of patients with cystic fibrosis. Also, clinical research on cystic fibrosis will continue to explore the pathogenesis of this disease and search for effective treatment methods.

The Institute intends to strengthen fundamental and clinical nutrition research studies. Other areas to be emphasized include studies of inherited diseases such as lysosomal storage disorders, cartilage and bone disorders, and sickle cell anemia; the genetic and immunologic bases of diabetes; the role of the immune system in systemic lupus erythematosus and rheumatoid arthritis; peptide-receptor interactions in the digestive tract and central nervous system; and the pathogenesis of various kidney diseases, especially those leading to end-stage renal disease.

● Research Training and Manpower Development

The development of a well-trained, highly qualified cadre of biomedical researchers is the most important ingredient of a productive research effort. Without such scientists and their original ideas, it would not be possible to capitalize on the unprecedented scientific opportunities which now exist nor to pursue future research developments. Physician-scientists have a unique role to play in this regard since their expertise encompasses both research methodology and clinical medicine.

The Institute plans to strengthen efforts in research training and manpower development, with particular emphasis given to the new Physician-Scientist Award Program. This Program encourages newly trained clinicians to develop independent research skills and experience in a fundamental science. Thus, clinically-trained professionals

with a commitment to research will have the opportunity to develop into independent biomedical investigators able to compete successfully for NIH research support.

II. Areas of Scientific Opportunity

● Immunology

Defects in immune mechanisms have been implicated in the cause or aggravation of a number of chronic diseases, such as rheumatoid arthritis, glomerulonephritis, insulin-dependent diabetes mellitus, inflammatory bowel disease, and several hematologic diseases. Researchers have linked these diseases to humoral and cell-mediated immune defects, including abnormalities in specific lymphocytes and in their interactions to regulate the immune system, endogenous and exogenous triggering mechanisms responsible for stimulating abnormal immune responses, and factors which predispose an individual to development of an abnormal immune response. Increased understanding of the immunologic basis of these diseases can be expected to promote prevention, diagnosis, and treatment of these and other diseases. For example, specific interventions targeted at specific immune defects which underlie these diseases can be anticipated. Advances in immunology are also being applied to improving immunosuppressive regimens, thereby improving survival rates in organ transplantation.

●● Immunology of Rheumatic Diseases

Researchers have developed new insights into the immunologic basis of some forms of rheumatic diseases and the interaction between immune dysfunction and inflammation, the hallmark of rheumatic diseases. The encounter of neutrophils with immune complexes and complement components has been linked to their secretion of lysosome hydrolases, which in turn produce tissue injury and provoke potent proinflammatory agents, most notably the newly characterized leukotrienes. Additional investigations will examine further the factors which activate neutrophils in the rheumatic diseases, factors such as immune abnormalities and the effects of leukotrienes and other products on inflammatory arthritis.

The occurrence of autoantibodies recognizing a number of specific nuclear and cytoplasmic antigens (RNP, Sm, Ro and La antigens) has been shown to be characteristic of autoimmune rheumatic disorders, particularly systemic lupus erythematosus. These findings are proving valuable in the diagnosis and management of this disease. In another exciting development, by administering monoclonal antibodies to double-stranded DNA in New Zealand mice, researchers were able to blunt initiation of autoimmunity and thereby prevent emergence of lupus nephritis in this animal model of systemic lupus erythematosus (SLE). Continuing research also aims to determine how activated B cells and defective T cells found in patients with SLE are related to immunoregulatory abnormalities in this disease.

●● Immunology of Insulin-Dependent Diabetes Mellitus (IDDM)

Recent evidence strongly suggests involvement of the immune system in the beta cell destruction which results in the loss of insulin production characteristic of insulin-dependent diabetes mellitus (IDDM). In clinical studies of IDDM, investigators have accumulated evidence of a rather extended prediabetic period during which beta cells are being destroyed and islet cell antibodies can usually be detected. If the relationship can be definitely established, immunosuppression in the prevention of IDDM may be a possibility.

●● Immunology of Kidney Diseases

In both primary and systemic glomerular diseases, immune complexes can be found in the glomeruli. The responsible immunologic mechanisms thus far defined involve either deposition of the immune complexes from the circulation or their formation in situ. Also, with the discovery of the importance of glomerular anionic sites, a new understanding of renal disease appears to be unfolding. Recent advances have shown that alteration of the electrical charge of the glomerular basement membrane, by altering the anionic glycoproteins or sulphated glycans, may be the primary process responsible for disease states characterized by proteinuria. Further exploration is needed to delineate the relationship of genetic factors, the complement system, physical and chemical aspects of the basement membrane, and the dynamic equilibrium of immune complexes to development of renal injury in kidney diseases.

●● Immunology of Digestive Diseases

In digestive diseases, two separate genetic regions have been shown to determine the murine T-dependent antibody response to A-gliadin, a wheat protein that activates gluten-sensitive enteropathy: H-2 on chromosome 17 and the immunoglobulin heavy chain allotype locus on chromosome 12. These findings in mice suggest that immune response genes coded by the major histocompatibility complex may control T-dependent humoral antibody and T-cell mediated immune responses to dietary gliadin in man. Continued detail work on the mechanisms responsible for the regulatory T-cell, macrophage, and B-cell responses elicited following exposure to a well-defined antigen such as gliadin would be of value in our overall understanding of the regulation of mucosal immune function.

●● Immunology of Transplantation

New information about the immunogenetics of rejection has improved survival rates and feasibility of liver, renal, and islet cell transplantation. A new approach to overcoming the problem of rejection in pancreatic islet allografts consists of

pre-immunizing the recipient with donor blood pretreated by ultraviolet light. This new treatment appears to induce donor-specific unresponsiveness to islet cell allografts without the use of immunosuppressive drugs and may prove useful for the transplantation of other types of tissue as well. More research is needed to determine whether this procedure is applicable to humans and whether such treatment will reduce or eliminate the need for immunosuppressive agents to maintain the transplanted tissue. Other research emphases include determining the mechanisms of the immunosuppressive effect of cyclosporine which can be maximally utilized in prevention of allograft rejection.

● Molecular Genetics

The use of new techniques of molecular genetics makes possible identification of genetic factors associated with increased risk for developing certain diseases, definition of specific gene defects in inherited disorders, and determination of the DNA sequencing of genes coding for substances of potential therapeutic value. Specific research foci for NIADDK in these areas include the structure and expression of the insulin, globulin, and collagen genes; synthetic production of hormones and other substances important for treatment of disease; prenatal diagnosis of certain hematologic and metabolic disorders; and HLA typing of populations at increased risk for developing diabetes, rheumatic diseases, connective tissue diseases, and skin diseases.

Advances in recombinant DNA techniques have already made possible synthesis of potentially unlimited amounts of insulin, somatostatin, and growth hormone. New understanding of post-translational modification has permitted elucidation of the prohormone and the pre-prohormone structure of insulin, somatostatin, and other pancreatic hormones. As the complexity of the underlying genetic bases and pathogenetic mechanisms of diseases are unraveled, enhanced understanding will lead to the potential for specific treatment and preventive intervention.

For example, there appear to be at least three distinct genetic forms of Type I, insulin-dependent diabetes, based on associations with specific genetically determined HLA antigens. Investigators have also made considerable progress in determining some of the different pathogenetic mechanisms involved in Type II, noninsulin-dependent diabetes (NIDDM). Some of these patients with NIDDM have been shown to have discrete point mutations in the human insulin gene, leading to a biologically inactive insulin. Most recently, scientists have utilized cloning and nucleotide sequence analysis of the insulin gene from such a patient to enable precise identification of the mutation.

Significant advances are being made in defining specific genetic, molecular, and biochemical defects in certain forms of osteogenesis imperfecta (OI), a heterogeneous genetic disorder producing various forms and degrees of fragile bone leading to fracture, even in utero. Through the use of cloned probes specific for unique genes and

related techniques, scientists have begun to define the genetic defect in this disease. As the underlying defects of osteogenesis imperfecta are identified, patient management may include replacing the specific deficient biochemical component or gene responsible for production of collagen and bone.

Defects in globin genes responsible for the various forms of thalassemia and sickle-cell anemia have been identified and have led to the recent breakthrough in control of gene expression in these diseases. Recent development of techniques to analyze nucleic acids has paved the way for improved methods of prenatal diagnosis of these diseases and ultimately of many other genetic disorders, utilizing analysis of DNA extracted from amniotic cells obtained by amniocentesis. Detection of abnormal DNA nucleotide sequences has been facilitated by the development of synthetic complementary DNA fragments to detect the mutation in the patient's DNA that results in the diseases. By replacing the more hazardous diagnostic method using fetal blood sampling with sampling of amniotic cells or chorionic tissue, the technical difficulty and risks are greatly lowered and the procedure can be performed at a much earlier stage of fetal development.

Hemochromatosis is an iron-storage disease associated with skin pigmentation, liver cirrhosis, diabetes, and other abnormalities; it is a progressive and fatal disease if not recognized and treated at an early age. Linkage has now been established between the hereditary hemochromatosis gene and HLA genes on chromosome 6, and the mode of inheritance has been determined to be recessive. Recognition of the mode of inheritance of this disease should lead to more frequent identification of homozygous individuals before onset of organ damage and end-stage disease, preventing serious illness, and should make possible the application of appropriate treatment.

New techniques have made possible determination of the gene mutations which produce the defective enzymes of several inherited metabolic diseases, including the Lesch-Nyhan syndrome, in which activity of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) is virtually absent. This syndrome is characterized by overproduction of uric acid, severe central nervous system disorders, and a compulsive form of self-mutilation. The gene structure of HPRT and its location on the X chromosome have been established. Also, the native, fully active human enzyme has been isolated, purified, and its amino acid sequence determined. Using this information, investigators have determined that HPRT deficiency diseases are often caused by single base mutations in the genes that lead to deleterious amino acid substitutions in the expressed enzyme. Understanding of the molecular basis of HPRT diseases will be instrumental in suggesting effective approaches to their treatment.

- Cell Biology

Determination of the fundamental processes involved in cell differentiation and growth, the nature and regulation of cell function, and the synthesis and secretion of hormones is essential for understanding

normal physiology as well as the etiology and pathogenesis of various diseases for which NIADDK is responsible. Of specific interest to NIADDK in this area are the post-translational events involved in the cell's processing of substances it produces or which are brought to it (metabolic diseases); the regulation of cell function by hormones, neural factors, and nutrients (endocrinology, diabetes, nutrition); and mechanisms of bone cell differentiation and growth (musculoskeletal diseases).

Defects and imbalances in the dynamic process of bone remodeling can lead to serious bone disorders such as osteoporosis, osteomalacia, and Paget's disease. Understanding the regulation of this process by local factors is a key to future developments in the field of bone diseases. The evolution, specialization, and migration of osteoblasts are controlled by a variety of local as well as systemic factors. Human skeletal growth factor is one protein that has shown the capacity to couple bone resorption and formation. Another protein, osteonectin, stimulates synthesis of collagen and other proteins, increases alkaline phosphatase activity, and may have a role in attaching bone mineral to the matrix.

It has recently become clear that a number of infectious diseases of the gastrointestinal tract are mediated by attachment of microorganisms to the intestinal mucosal surface of the host. Evidence suggests that, in some cases, the mucosal adherence is mediated by interaction between a specific component on the surface of bacteria and a specific receptor site at the mucosal surface of the host. Rapid progress has been made in localizing the colonization factor antigens (adhesins) of bacteria to a class of hair-like appendages termed pili or fimbriae. Research now shows that specific receptors on the gastrointestinal surface of the host which mediate adherence are genetically determined, age related, and that they vary at different levels of the gastrointestinal tract. These results provide a molecular basis for understanding levels of colonization, age related onset of diseases, and resistant and susceptible host populations. Importantly, there are a number of points at which it may be possible to interfere with the early stages of infection.

In similar research in the urinary tract, scientists are assessing the potential role of P-fimbriated bacteria in pyelonephritis. Advances are expected to multiply as more investigators obtain the techniques needed for quantifying the presence or absence of kidney receptors for such bacteria and can delve into the physiology of such receptors. An important conceptual advance has occurred in viewing hepatocytes as heterogeneous in structure, enzyme content, and function in accordance with their location in the liver lobule. Methodological advances have allowed separation and analysis of liver cells in specific locations in the liver acinus. Much additional quantitative data will be sought on the biochemical activities of the liver cells in the various acinar zones. This information may be helpful in localizing pathophysiologic changes in bile salt transport, drug metabolism, and glycogen metabolism and storage in the liver acinus.

Micropuncture of the bile canaliculus may open up the understanding of bile secretion in the same manner as micropuncture of the renal tubule clarified the understanding of renal physiology. Future research may provide information on ion movements and other aspects of bile secretion.

Keratins are a group of high molecular weight proteins formed in the epidermis of humans and other animals. Application of immunologic, molecular genetic, and cell culture techniques has yielded much information about the structure and function of the epidermal keratins and their expression during differentiation, embryonic skin development, and in certain disease states. Several levels of control mechanisms for the process of keratinization have been demonstrated, including post-translational modification, gene control associated with the degree of differentiation, and the effect of small molecular weight molecules such as vitamins and hormones. It is now also possible to analyze for abnormal keratins by the presence of their messenger RNA before the keratin itself is phenotypically visible in the epidermis. These basic advances have the potential for improving pre- and post-natal diagnosis and treatment of numerous skin diseases.

Important advances have been made recently in the characterization and structural studies of the insulin receptor and its insulin-mediated phosphorylation. These studies also demonstrated that insulin-mediated phosphorylation is one of the earliest steps in insulin action following the binding of the hormone to its receptor. Further research is needed in many cell types to elucidate the biosynthesis and function of the insulin receptor and the relationship of the subunits to its function. Additional research is also needed to determine the functional implications of phosphorylation of the insulin receptor.

Also under intense study is the process through which newly synthesized insulin is either stored or secreted. The fine details of synthesis, compartment storage in secretory granules and vesicles, and the regulation of the secretion event are in the process of being deciphered. Investigators have concluded that exposure to high concentrations of glucose during the critical time of transfer of insulin to secretory vesicles "marks" those vesicles for immediate release of hormone at a subsequent glucose challenge. Understanding how the cell "marks" and recognizes "marked" vesicles would be of significance in furthering our knowledge of the modulation of the secretory apparatus in response to various stimuli. The ability to influence and control insulin secretion to maintain euglycemia is particularly useful for treatment of certain forms of non-insulin-dependent diabetes.

- Integrative Physiology

Recent research has permitted a glimpse of a more complex inter-relationship among cells than traditionally believed. In the past,

the anatomical and morphological differences between the endocrine and nervous systems, the two main systems devoted to intracellular communication in man, led to their characterization as separate entities. Evidence from studies in man and lower level organisms, however, has accumulated to strongly suggest modification of this view. These studies indicate considerable overlap between the endocrine and nervous systems and have introduced a third system, the paracrine, to create an overall concept of cellular integration in man. All three systems have in common basic biochemical elements: messenger molecules, their receptors, and post-receptor effects on target cells. The function of the molecule differs then with the differentiated nature and location of the secretory cells and the arrangement of the extracellular fluid space carrying the messenger molecule to the target cell.

Further research is needed to elucidate the mutual influence of endocrine organs and the central nervous system, the modification of secretory activities of one hormone-producing cell by the secretions of another, and the implications of differentiated cells retaining the capacity to produce all the proteins encoded in their genetic material throughout their lives.

A prime example of the scientific opportunities in this area is the new understanding of integration of gastrointestinal function. Researchers have identified several gastrointestinal peptides with significant hormonal effects on several sites within the digestive tract, the liver, and the pancreas. These findings lend support to a concept of the digestive tract integrated by both the endocrine and nervous systems. Studies are being encouraged to determine the physiologic significance of these central nervous system peptides and to characterize their role in interaction between the central nervous and digestive systems. Further studies will aim to elucidate additional hormone and receptor interactions and kinetics in this system.

Work assessing neural control of the lower esophageal sphincter has highlighted the importance of non-adrenergic and non-cholinergic transmitters in activation of smooth muscle in the digestive tract. Important advances have also been made in characterizing the anatomy and neurophysiology of the myenteric plexus of the intestine. A variety of neurohumoral transmitters which are released in response to nerve stimulation have been identified in the myenteric plexus, indicating the importance of these neurohumoral compounds as well as direct neural stimulation in regulating gastrointestinal motility.

A number of physiological processes interact in the transport of urine from the kidney, storage in the bladder, and micturition. Research advances have suggested that adenosine triphosphate may function as a neurotransmitter in regulating urethra sphincteric control and bladder contraction in the cat. Basic neurophysiological and neuropharmacological studies will continue to be stressed in this subject.

Significant progress has been made in unraveling the complex interaction among various hormones regulating glucose metabolism. Recent studies have produced a major breakthrough in understanding how glycolysis and gluconeogenesis are reciprocally controlled through alterations in key regulatory enzymes. Research results suggest that the action of insulin opposes the action of glucagon (and epinephrine) by affecting a bifunctional enzyme which controls the level of fructose-2, 6-biphosphate. This compound is also present in many other tissues and cells and its overall impact remains to be discovered.

A related area of research emphasis is the mechanism of action of counterregulatory hormones, especially their relation to glucose homeostasis and the development of the complications of diabetes. Maintaining euglycemia involves several mechanisms, some involving insulin and its counterregulatory hormones, glucagon and epinephrine. Some diabetics have developed defects in their glucagon and epinephrine responses that blunt or prevent glucose recovery from hypoglycemia. Evidence indicates that epinephrine secretion is diminished as a result of diabetic autonomic neuropathy. Recent efforts have been successful in identifying diabetics with such impairment, who are therefore at risk for recurring episodes of hypoglycemia during intensive insulin treatment.

Another promising research area involves the development and design of biologically superactive and superstable synthetic peptides. A stepwise design approach has successfully produced a synthetic derivative of alpha-melanotropin, a superactive peptide shown to have potential for therapeutic function on the neuromuscular system in multiple sclerosis and progressive spinal atrophy.

Researchers have shown that some growth hormone deficiency is due to hypothalamic growth hormone releasing factor (GRF) deficiency rather than deficiency of growth hormone (GH). This work shows that GRF may be a substitute for treatment in some children with hypopituitary short stature. Since the molecule for GRF is shorter than that of human growth hormone (44 amino acids vs. 194 amino acids), it is more easily synthesized and may be made available for future clinical use.

Scientists investigating exocrine sweat gland function have suggested that the dual innervation of the gland provides a profound control mechanism for regulating the function of both the duct and the secretory portion of the gland. One of their findings was that the secretory portions of cystic fibrosis sweat gland are abnormal in their response to beta adrenergic stimulation. Previous to this finding the only demonstrated defect in this disease was abnormal ductile function.

NATIONAL CANCER INSTITUTE

I. Major Program Changes, FY 1986

● Research

Basic studies will be expanded in the most promising areas of research including monoclonal antibodies, oncogenes, chemoprevention, biochemical epidemiology, drug resistance in cancer, human T-cell leukemia, lymphoma virus, biochemical approaches to cancer invasion and metastasis, and the physiological cellular mechanisms which contribute to the generation of different cell populations in tumors. Outstanding Investigator Awards will be initiated to provide investigators with a renewable five-year award to conduct research.

Specific areas of expansion/emphasis in each of the four research thrusts follow:

1. Cause and Prevention Research

- Development of a statistical reporting system for cancer incidence in areas not covered by the NCI Surveillance Epidemiology and End Results Program.
- Integration of biochemical and molecular laboratory determinations with more classic epidemiologic approaches in order to predict cancer risk on an individual basis instead of on a population level, and prior to onset of clinically evident cancer.
- Determination of the metabolism of chemopreventive agents.
- Oncogene research including development of novel test systems for oncogene activity.
- Development of vaccines in three main areas: human T-cell leukemia/lymphoma virus; hepatitis B virus associated with the development of primary hepatocellular carcinoma; and Acquired Immune Deficiency Syndrome (AIDS).

2. Detection and Diagnosis Research

- Application of molecular biology and genetics to develop effective techniques for early detection of cancer through identification of people who are at greatly increased risk.
- Evaluation and comparisons of multiple new diagnostic imaging modalities.

3. Treatment Research

- Expansion of clinical trials efforts to better accommodate the increasing number of new active anticancer drugs and biologics.
- Testing hypotheses relating to the potential efficacy of peri-operative chemotherapy, high doses of drugs, the interdigitation of radiotherapy and cytotoxic agents, and the use of non-cross resistant combinations.
- Investigations of the mechanism of clinical drug resistance.
- Design of novel or modified agents to circumvent or overcome drug resistance.
- Development of in vitro assays to predict tumor resistance to drugs.
- Expansion of clinical cooperative group research to strengthen the network in place to apply research results and to support clinical research in photoradiation therapy, intraoperative radiotherapy, anticancer agent development, and utilization of combined modality and adjuvant therapy treatment.

4. Cancer Biology

- Development of immunologic probes to investigate the interaction of carcinogens with DNA in the cell.
- Investigation of the physiological cellular mechanisms which contribute to the generation of different cell populations in tumors.
- Utilization of monoclonal antibodies to define the factors that determine biochemical individuality in carcinogen susceptibility and lead to "high-risk" individuals.

● Resource Development

1. Centers

Additional cancer center core grants will be awarded in order to enhance the network of national resources for the prompt transfer of laboratory findings into clinical research and treatment. Emphasis will be placed on improving patient access and locating centers in minority populated communities which appear to be at greater risk of developing certain types of cancer. Efforts will be expanded to further develop and strengthen the links between centers and community cancer programs.

2. Manpower Development

The proposed budget for research manpower development will support additional training that cuts across all areas of cancer research, including its cause and prevention, detection and diagnosis, and treatment. Emphasis will be placed on surgical and radiation oncology, including diagnosis and prevention oncology, and the cancer control sciences which seek to promote rapid and effective application of basic, clinical, and epidemiological research findings to large segments of the population.

3. Construction

Increased funding for the Construction Program will support renovation of basic research laboratories to upgrade biohazard containment facilities and animal facilities to meet mandatory DHHS standards for animal care. Clinical laboratories will be renovated to facilitate new technologies and diagnostic measures such as ultrasound, preclinical tumor immunology, hyperthermia, and tumor imaging such as nuclear magnetic resonance. Additional facilities at cancer research institutions will also be provided.

● Cancer Control

The primary focus of cancer control will be in the area of prevention. The NCI has set a goal of achieving an overall 50 percent reduction in cancer mortality rates by the year 2000, and cancer control activities will play a major role in the attainment of this goal.

With cigarette smoking responsible for at least 30 percent of all cancer mortality, the Smoking, Tobacco and Cancer Program (STCP) will play a prominent role in achieving the Institutes' goal. Smoking cessation will be a major focus of the STCP; however, in order to assume that cancer mortality continues to decrease beyond the year 2000, smoking prevention will also receive a major emphasis.

Special emphasis will be given to nutritional studies that clarify the role of dietary fat, fiber, micronutrients, and food additives in cancer etiology. A number of specific diets will be studied in humans to determine their ability to reduce the incidence of cancers at one or more specific body sites. The effect of dietary modification or nutritional supplements on cancer incidence will be investigated.

Chemoprevention will receive a high priority. Evaluation studies to determine the chemopreventive effects of the addition of beta-carotene; vitamins A, C, E; and synthetic retinoids to the diet will be initiated.

The Cancer Control Science Program will be increased to assure an orderly sequence of research on cancer control interventions to promote the rapid and effective application of basic clinical and epidemiologic research findings in large segments of the population.

Expansion will occur in the Community Clinical Oncology Program as well as analysis of cancer control across the country to determine progress toward the NCI goal and objectives. Also, additional support will be given to rehabilitation, continuing care problems, and the needs of cancer patients occurring during and after treatment. This will include emphasis on selected aspects of cancer pain and management therapy.

II. Areas of Scientific Opportunity

● Oncogenes

Efforts to elucidate the genetic alterations that lead normal cells to become cancer cells have been aided immeasurably by the investigation of acute transforming retroviruses utilizing technological advances in the area of molecular biology. Acute transforming viruses have substituted viral genes required for replication with discrete segments of host cellular information. When incorporated within the viral genome, these transduced sequences, designated oncogenes, acquire transforming properties.

In the past few years, evidence has emerged that some of the very same normal cellular genes which have given rise to retroviral oncogenes can be activated as transforming genes by mechanisms completely independent of retrovirus involvement. There is also evidence that has linked some of their cell-derived transforming genes to cellular genes activated to become oncogenes of human cancer cells.

Acute transforming retroviruses can cause a variety of malignancies, including sarcomas, carcinomas and hematopoietic tumors. In tissue culture, these agents rapidly induce growth alterations in susceptible target cells. Such transformants, after propagation in culture, produce tumors in animals, whereas uninfected cells in parallel cultures do not. Thus, the induction of transformed foci by the virus directly reflects its tumor-inducing capability in vivo.

Advances in recombinant DNA technology have made it possible to clone the proviral forms of these RNA viruses. The retrovirus genome contains long terminal repeat sequences, designated LTRs, which possess signals for the initiation, enhancement, and termination of transcription. However, the prototype acute transforming virus has deleted substantial information necessary for replication functions and has substituted, instead, a discrete new segment of information. Specific alteration or deletion of the substitution sequence causes the virus to lose its ability to transform cells or cause tumors. Analogous findings with a number of acute transforming viruses have led to assignment of the viral transforming function(s) to the acquired onc sequence.

If a retroviral onc sequence is used as a DNA probe to analyze normal cellular DNAs, the probe detects homologous sequences in DNAs of a wide range of vertebrate species. These findings, in addition to the fact that consequences are generally represented at single copy

numbers, imply that viral oncogenes have arisen from normal cellular genes. Evidence that these genes, designated proto-oncogenes, are also conserved in evolution further implies that they serve very important functions in normal cellular processes.

If any of the thousands of genes that exist in our cells could acquire neoplastic properties when captured by one of these viruses, then we would never expect to observe the same sequence incorporated by more than one of the known two dozen or so acute transforming retrovirus isolates. In fact, several virus isolates from the same or even different species have captured the very same onc sequence. These findings have indicated that the number of cellular genes that can acquire transforming properties when incorporated within the retrovirus genome must be rather limited.

Investigations aimed at elucidating the functions of the cellular genes that give rise to onc genes have in some cases led to detection of their transforming proteins. With one group of onc genes, the prototype of which is the src gene of Rous sarcoma virus, it has been possible to assign an enzymatic activity to the gene product. These genes code for protein kinases having specificity for tyrosine residues. However, identification of the function of proto-oncogenes from which onc genes have arisen has, until recently, not been effected.

Studies with simian sarcoma virus (SSV), the only acute transforming retrovirus of primate origin, have been particularly informative. Having developed an appropriate biologic system for SSV characterization, the SSV genome was cloned, its structure dissected, and its cell-derived onc gene, v-sis, identified. Subsequently, the nucleotide sequence of the complete SSV genome was determined, and a protein (p28sis) established as the product of the SSV transforming gene. It has been found that the v-sis oncogene is very closely related to a gene coding for platelet-derived growth factor (PDGF).

Human PDGF is a potent mitogen for connective tissue cells, and is biologically important because it is thought to be involved in wound healing. Amino acid sequencing studies have shown that 87 percent of the amino acid sequence determined for PDGF matched that predicted for p28sis. Thus p28sis and PDGF appear to be derived from the same cellular gene.

Since genes related to retroviral onc genes are present in human DNA, it became possible to assess the role of proto-oncogenes in the etiology of human cancers. One approach has involved the chromosomal mapping of human proto-oncogenes, and this approach has indicated that proto-oncogenes are widely distributed throughout the human genome. Thus, sis has been assigned to chromosome 22, the oncogenes mos and myc to chromosome 8, and myb to chromosome 6. Members of the ras oncogene family are found on chromosomes 1 (N-ras), 6 (K-ras), 11 (H-ras-1), and 12 (K-ras-2). Additional proto-oncogenes have been localized to chromosomes 3 (raf-1), 4 (raf-2) 5 (fms), 15 (fes), 22 (abl), and X (H-ras-2). That specific chromosomal rearrangements

were known to occur in certain human tumors raised the possibility that onc genes might be activated by chromosomal translocations. Indeed, chromosomes harboring onc related genes have been shown to be involved in several such diseases.

Chronic leukemia viruses lack a specific onc gene sequence. Recent studies have provided evidence that their mechanisms of malignant transformation involve the activation of cellular proto-oncogenes by the nearby integration of regulatory sequences located within the viral LTR. Recent studies have also provided evidence for oncogene activation in naturally occurring tumors by transposition of endogenous cellular DNA sequences containing regulatory signals.

Another approach toward detecting transforming genes was initiated a few years ago. By the use of a sensitive technique for incorporating exogenous DNA into cells, termed DNA transfection, investigators asked whether DNAs of animal or human tumor cells possessed the capacity to directly confer the neoplastic phenotype to a susceptible cell. Such results might indicate the presence of a "transforming gene" in the tumor. In fact, a number of human tumor DNAs have been shown to induce transformed foci in the continuous NIH/3T3 mouse cell line, which is highly susceptible to the uptake and stable incorporation of exogenous DNA.

Many human oncogenes that have been detected by transfection analysis are related to a small group of retroviral oncogenes, designated ras. Although these oncogenes arise from different cellular genes, sequence comparison and immunologic analysis of their protein products revealed their high degree of homology and, hence, evolutionary relatedness.

The availability of molecular clones of the normal and activated alleles of human ras proto-oncogenes now makes it possible to determine the molecular mechanisms responsible for the malignant conversion of these genes. The genetic lesions responsible for activation of a number of ras oncogenes have been localized to single base changes in their p21 coding sequences. In the T24/EJ bladder carcinoma oncogene, a transversion of a guanine to a thymine causes a valine residue to be incorporated instead of a glycine into the 12th position of the predicted p21 primary structure. Another oncogene designated Hs242, from a human lung carcinoma, has also been identified as an activated H-ras (human) proto-oncogene, making it possible to compare the mechanisms by which the same human proto-oncogene has been independently activated in human tumor-derived cells.

The position of the genetic lesion in Hs242 leading to its malignant activation has been identified and it was found that the Hs242 oncogene and H-ras (human) differed by a single base. This base change (adenine to thymine) resulted in the replacement of glutamine by leucine in this codon. Thus, a single amino acid substitution seems sufficient to confer transforming properties on the product of the Hs242 oncogene. These results also established that the site of activation in the Hs242 oncogene was totally different from that of the T24/EJ oncogene.

Subsequent studies have assessed the generality of point mutations as the basis for acquisition of malignant properties by ras proto-oncogenes by molecularly cloning and analyzing other activated ras oncogenes. Thus far it appears that mutations at positions 12 or 61 may be the genetic lesions most commonly responsible for activation of ras oncogenes under natural conditions in human tumor cells.

There is a great likelihood that not all of the proto-oncogenes capable of being activated as oncogenes have been discovered. Moreover, genetically predisposing states certainly exist but likely involve recessive alterations whose effects are more subtle than that of the germ line transmission of an activated oncogene. Finally, the few genes which have already been identified as targets of the neoplastic process are highly conserved and in their unaltered state almost certainly are involved in essential growth processes. Thus, any attempt to intervene in such normal functions is likely to be difficult. Nevertheless, the evidence obtained so far strongly argues that the problem of deciphering the neoplastic process is becoming less complex and, thus, more approachable. If so, it is likely that continued investigation of this small group of proto-oncogenes will provide important insights into strategies that may eventually be useful in the diagnosis, treatment, and it is hoped even prevention of human cancer.

Recent investigations have identified a small set of cellular genes which appear to be frequent targets for genetic alterations leading to human cancer. These findings offer an unparalleled opportunity to determine the important pathways involved in the neoplastic process. Future efforts will be directed at determining the mechanism(s) responsible for the activation of oncogenes in human cancers. A major focus will be on identifying the cellular targets of oncogenes which can be activated by chemical mutagens and viruses, thus unifying cancer causation and relating these to environmental factors as well. To this end, additional normal oncogenes and their functions will be identified, and normal and abnormal oncogene products will be compared to determine at which stage abnormalities occur. Using this approach it may be possible to interrupt this process by biochemical and/or genetic means. Since it is now possible by recombinant technology to make large quantities of cloned oncogene products, attempts will be made to identify specific purified oncogene products and to determine their structure and active site(s). With such knowledge, it may be possible to design specific inhibitors to interfere with their mode of action. Specific probes will be developed that will enable the characterization of specific tumors yielding additional and sensitive molecular-diagnostic tools for the pathologist. The diagnostic use of oncogene probes may also make it possible to relate various tumor-related events and oncogene protein expression to specific tumor types, resulting in a tumor "map." Complete maps may some day be developed relating unique tumor parameters to specific molecular events that can be evaluated diagnostically using oncogene markers.

● Biochemical Epidemiology

Biochemical and molecular epidemiology is an important multidisciplinary area in cancer research which combines epidemiologic and experimental approaches. For some time it has been clear that the traditional methods of epidemiology and laboratory research provide valuable information as to cancer etiology, but each approach alone has its limitations. By integrating laboratory and epidemiologic methods it is becoming possible to evaluate certain cancer risk factors that are difficult to detect and characterize by either experimental or epidemiological approaches. These include dietary and metabolic factors, genetic susceptibility, air and water pollutants, oncogenic viruses, environmental and occupational factors, and several other potential etiologic factors. Biochemical epidemiology provides an opportunity to clarify cancer risks associated with tissue levels of environmental carcinogens and their metabolites, to assay for markers of early response to carcinogens, to provide insight into carcinogenic mechanisms and host-environment interactions, and to determine the biologically effective dose of carcinogens in man. Considerable progress has been made in developing and utilizing laboratory probes that may help to elucidate cancer risks including techniques to assess specific host susceptibility factors; assays to detect carcinogens in human tissues, cells and fluids; cellular assays to measure pathobiological evidence of exposure to carcinogens; and methods to measure early biochemical and molecular responses to carcinogens. Of special interest is an approach which measures the interaction of specific agents with cellular target molecules, for example, through adduct formation with proteins and nucleic acids, excretion levels of excised adducts or markers of oncogene expression.

Several potential markers are available for measuring the extent of human exposure to carcinogens and for assessing the biologically effective dose of carcinogens in humans. For example, carcinogen adduct formation with nucleic acids can be detected by radioactivity, fluorescence, high pressure liquid chromatography and by new immunologic techniques. Similarly, measurement of carcinogen adduct formation with proteins is now feasible as exemplified by the alkylation of hemoglobin by ethylene oxide. Another potentially useful marker for detecting exposure to carcinogens is the urinary excretion of excised DNA adducts, and several methods for detecting DNA damage and repair (unscheduled DNA synthesis, strand breaks) are also available. These and other newly developed laboratory techniques, when combined with epidemiologic studies, will lead to more effective and accurate methods for performing quantitative risk assessments for various environmental chemicals.

There is a growing awareness that many cancers result from the combined effects of multiple environmental exposures (including initiators, promoters, and inhibitors), and the interaction of environmental factors with host susceptibility states. This is consistent with multistage models in which different risk factors accelerate the transition rates at various stages of carcinogenesis. Recognition of these concepts greatly expands the potential for

identifying causal factors and intermediate points along the causal pathway, and for applying preventive measures to reduce the risk of developing or succumbing to cancer. The approach of biochemical epidemiology is now focusing on the relationship between various common epithelial cancers and dietary factors, including micronutrients (e.g., vitamin A) and trace metals (e.g., selenium) that may be measured by serological assays, as well as macronutrients (e.g., dietary fat) that may affect the risk of certain neoplasms through hormonal perturbations. This approach may be useful for identifying groups or individuals at unusually high risk for cancer so that they can receive appropriate medical surveillance and/or become enrolled in intervention or prevention trials. The laboratory measures used in etiologic studies may also be incorporated in intervention projects designed to halt or reverse the process of carcinogenesis (e.g., chemoprevention). Biochemical and molecular measurements are being utilized to better characterize exposure to carcinogens. Such measurements include evaluation of the body burden of chemical carcinogens in studies of occupational and general environmental cancer risk factors, and determination of genotoxic damage and oncogene activation in the cells of individuals at high cancer risk. In addition, most human cancer cells have chromosomal or other genetic changes arising from inheritance or damage by environmental agents. With the development of new tools for the molecular dissection of human genes, there is reason to believe that human "cancer genes" will be identified in the near future, thus enabling newer approaches to preventing, detecting, and treating cancer. Recent laboratory advances have been utilized in epidemiologic studies to clarify the role of a newly discovered retrovirus, HTLV, in the development of adult T-cell leukemia, and this agent as well as others may also be involved in the recent outbreaks of the acquired immunodeficiency syndrome (AIDS) associated with Kaposi's sarcoma and opportunistic infections.

Biochemical epidemiology ranges from experimental research aimed at developing and refining laboratory procedures for use in human population studies, to epidemiologic studies incorporating laboratory probes shown to be safe, accurate, reliable and informative. This strategy enables the incorporation of emerging techniques in carcinogenesis research and molecular biology into epidemiologic investigations in order to elucidate cancer risk factors, including susceptibility states, past exposure to specific agents, and sub-clinical responses to initiators, promoters, and inhibitors of carcinogenesis. The task of identifying the full gamut of environmental, life-style, and host determinants of human cancer is obviously formidable. However, continued progress in the field of biochemical epidemiology should help surmount barriers and hasten discovery of the origins and the means of preventing cancer.

The NCI will continue support for pursuing newly emergent leads about the causes of cancer in human populations, using the biochemical epidemiologic approach. Future research will be expanded to include drug probes for predicting an individual's capacity for metabolizing carcinogens, measurement of carcinogen-metabolizing enzymes,

carcinogen-DNA adduct formation, DNA repair, gene polymorphisms, oncogene activation and cell surface antigenic changes.

- Human T-cell Leukemia/Lymphoma Virus

In 1980, researchers at NIH reported the first isolation of a human RNA tumor virus called HTLV (human T-cell leukemia/lymphoma virus). This novel retrovirus appears to be acquired by infection rather than genetic transmission and is associated with adult T-cell leukemia (ATL). The discovery of HTLV provided the opportunity to conduct epidemiologic studies of ATL and related diseases and served as a model by which other virally transmitted human cancers can now be identified. Recent seroepidemiologic studies have demonstrated that HTLV is endemic in areas of Japan, West Indies, Southeast USA, China, USSR, Africa, Malaysia, and Central and South America. A high percentage of relatives of persons with ATL have antibody to HTLV and/or the virus itself. Non-related persons living in endemic areas have a considerable incidence of exposure to HTLV, as determined by anti-HTLV antibody titers. Further studies are currently in progress on both the biology and epidemiology of HTLV. The recent availability of molecular clones to HTLV DNA will allow progress to be made in understanding the molecular biology of HTLV as well as its interaction with the host T-cell. This is of practical importance to the field of cancer research, since the identification of a virus which causes a human cancer will not only allow studies of the development of malignancy at a molecular level, but also raises the very real possibility that a vaccine to specific cancers might be developed.

Until recently, the search for a retrovirus in association with human cancer was negative. The discovery of T-cell growth factor in 1976 enabled the long-term culture of relatively mature T-cells, which in turn enabled the identification of HTLV in T-cell lymphoma cell lines. The availability of this system offers unprecedented opportunity in a number of related areas. It is now possible to determine the course of events, starting with virus infection, which induce these diseases with the ultimate goal of successful intervention or prevention of the disease. The availability of HTLV also gives the unique opportunity to study precisely the epidemiology of ATL and related diseases, and to identify some of these disorders as a single and unique clinical entity.

HTLV appears to be involved in the etiology or causation of ATL and other T-cell cancers. It is particularly prevalent in regions when ATL is endemic. Further, HTLV is detectable in 90-100 percent of patients with the disease, and patient relatives or cohabitants have a high rate of sero-positivity. HTLV is specifically present in malignant T-cells, and infection of normal T-cells in vitro confers a malignant phenotype. Although the virus appears to be transmitted by infection, it is not highly contagious. Infection seems to occur primarily through prolonged intimate contact, as within families, possibly by sexual contact or intermediate insect vectors, and probably by transfusion of blood from infected persons. Thus, research areas of high priority include determination of where HTLV

is found, what diseases are similar, or associated, how the virus is normally transmitted, and how it induces malignancy. Even if HTLV has been in and around humans for some time, the modern practice of blood transfusion and travel of people to endemic areas may extend the geographic range of this virus. The importance of this work is emphasized by the recent identification of HTLV-III as the likely etiologic agent of Acquired Immunodeficiency Syndrome (AIDS). This discovery has allowed the immediate development of diagnostic serology which will protect the nation's blood supply against transfusion-associated AIDS and holds the promise of an effective vaccine for high risk individuals.

- Drug Resistance in Cancer

The development of drug resistance by malignant cells is both a common clinical problem and an area of active research interest. Although the discovery and clinical evaluation of anticancer drugs has contributed substantially to dramatic increases in cure rates and survival for some types of cancer, many tumors eventually escape control. Combinations of drugs which act at different biochemical sites and have non-overlapping host toxicities have been useful in increasing initial response and cure rates or delaying time to relapse. While recurrent disease may respond to different drugs or drug combinations, clinical experience suggests that patients who relapse (despite initially effective aggressive chemotherapy) are less responsive to alternative regimens using presumably non-cross-resistant agents. This clinical observation has an in vitro parallel in the model of pleiotropic drug resistance (PDR). It has been repeatedly demonstrated that tumor cells selected for resistance to a single drug may develop simultaneous cross-resistance to structurally unrelated compounds with dissimilar mechanisms of action. Of importance, many of the agents to which cross-resistance is expressed include drugs in common clinical use, frequently administered together in combination drug regimens. Preliminary studies to determine a single explanation for PDR suggest that resistant cells have impaired ability to accumulate or retain drugs, although the precise mechanism of this "altered permeability" remains speculative. Other forms of single drug resistance, particularly those involving amplification or deletion of target proteins and enzymes responsible for drug degradation or activation are better understood from a purely biochemical standpoint, but their relevance to clinical drug resistance has not been firmly established by the necessary prospective studies to correlate response with tumor cell biochemistry. Thus, the continued development of clinically effective anticancer drugs requires the study of models designed specifically to discover drugs capable of overcoming resistance to treatment.

Animal tumors resistant to most individual antitumor agents have been developed under treatment selection. For them, there is extensive data on cross resistance and collateral sensitivity. The establishment and characterization of tumor cell lines from clinically drug-resistant patients will potentially allow development of similar

information on clinical cross-resistance and sensitivity as well. A base of specific drug-resistant animal and human tumors provides the opportunity to develop a data profile for new drugs and aid in planning Phase II clinical trials where heavily pretreated patients are often treated. Moreover, recent work has suggested that tumor cells selected for PDR may develop novel and specific membrane glycoprotein changes. The characterization of membrane changes associated with the development of the resistant phenotype may be useful both as a marker as well as potential target for monoclonal antibodies, with attendant diagnostic and therapeutic implications. The application of the techniques of molecular biology to resistant tumor cells derived both in vitro and in vivo has elucidated important basic knowledge about the genetics of drug resistance and the stability of the resistant phenotype. Such data will have direct implications in determining: (1) why resistance is inducible in tumor cells but not normal proliferative tissues; (2) what factors increase the frequency of drug resistance; and (3) whether there are specific clinical strategies to discourage the outgrowth of resistant clones or reverse resistance once it has occurred.

The present understanding of tumor cell drug resistance at the clinical level is incomplete and fragmentary. It is clear that both in animal models and in the clinical setting, there is an inverse relationship between tumor cell burden and curability. Using principles initially developed in anti-microbial research, Goldie and Coldman have developed a mathematical model for drug resistance in tumor cell populations in which the likelihood of finding a single cell with resistance to a specific agent is related to both population size and mutation frequency. Resistant cells are not "induced" by the toxic agent, but rather occur spontaneously as mutants at a predictable frequency in cell populations. Drug exposure provides a positive selection pressure allowing the resistant cells to outgrow the sensitive cell population. Thus, understanding the frequency, etiology, development, and reversibility of resistance is of utmost importance as the presence of even a single resistant cell may ultimately lead to treatment failure.

● Monoclonal Antibodies

Monoclonal antibodies (MoAbs) are produced by fusing an immortal myeloma cell line with an antibody-producing B cell. Hybridoma technology, a type of somatic cell hybridization, has become routinely used to produce MoAbs as research, diagnostic and therapeutic tools. These "hybrid" cells are capable of producing a theoretically unlimited supply of immunologically pure antibody with specific receptor recognition capacity. Evidence suggests that specific tumors and drug-resistant cancer cells may express novel surface antigens. Thus, the availability of appropriate MoAbs capable of recognizing cancer cells will have broad diagnostic and therapeutic implications. MoAbs have been developed to a large number of tumor types, and this is the first year that a substantial number of these reagents will be available for clinical use.

MoAbs have potential usefulness in basic research as well as diagnostic and therapeutic cancer care. In the basic sciences, MoAbs have been useful in determining the embryologic origin of specific leukemias and lymphomas and have shown derangements in functional lymphocyte subsets associated with Acquired Immunodeficiency Syndrome (AIDS) and their relationship to subsequent development of opportunistic infection and cancer. In the area of cancer diagnosis, radiolabelled MoAbs targeted to tumor cells will be used to improve diagnostic imaging techniques in specific cancers, such as melanoma and colon cancer. A newly developed MoAb to estrogen receptor has been screened as an improved quantitative measure for the detection of this receptor in breast cancer cells. It is anticipated that this new assay will contribute to more sensitive diagnosis and thus, improved treatment of breast cancer. Further, it has recently been demonstrated that a MoAb (OC125) which recognizes a surface glycoprotein of ovarian cancer cells may be useful in following disease response in patients with ovarian cancer. The recent availability of this sensitive and non-invasive diagnostic technique will permit appropriate decision-making in the treatment plans of individual patients with less reliance on invasive diagnostic techniques. In the area of treatment research, MoAbs either alone or conjugated to toxins are being evaluated in a clinical trial involving patients with metastatic melanoma. Lymph node disease may be especially susceptible to MoAbs introduced directly into lymphatics via subcutaneous injection. This route improves sensitivity and localization of the antibody while decreasing host toxicity and may be useful in patients with melanoma, breast cancer and colon carcinoma. Taken together, this improvement in therapeutic index may dramatically improve the antitumor effects of reagents with minimal activity via intravenous injection. MoAbs are also being used to eliminate tumor cells in patient bone marrows in vitro prior to autologous bone marrow transfusion. In addition, MoAbs may be used to deplete donor marrow of mature T cells, thus reducing the incidence and severity of graft vs. host disease, an important complication in syngeneic bone marrow transplantation.

The obvious potential for MoAbs in the areas of basic tumor cell biology, cancer diagnosis, and clinical cancer care make this an area of cancer biology which merits special emphasis. Current difficulties in using a foreign (mouse) antibody as a diagnostic/therapeutic reagent in man may be eliminated by the development of human cell lines of plasma or B-lymphocyte origin capable of serving as fusion partners for the production of human-human hybridomas synthesizing human MoAbs. In addition, further developments in this area may have far-ranging implications in medical disciplines within and outside of oncology. MoAbs directed against incompatibility antibodies (anti-idiotypic antibodies) have recently been generated and their role in transplantation immunity is under study. This may provide improved methods of management of both organ rejection and graft vs. host disease in tissue and bone marrow transplantation respectively.

● Chemoprevention

The chemoprevention of cancer is a new research thrust to see whether natural or synthetic agents can lower cancer incidence. The growing body of basic and epidemiological evidence on the inhibition of cancer suggests that chemoprevention merits an aggressive research effort.

Potential chemoprevention agents include several naturally occurring substances found in many foods, such as vitamin A and its precursor beta-carotene, vitamins C and E, and the trace metal selenium. Other agents under study in the laboratory include phenolic antioxidants, protease inhibitors, prostaglandin synthesis inhibitors, indoles, and uric acid.

In one of the earliest laboratory studies in 1955, Lasnitzki showed that precancerous changes in mouse prostate cells grown in vitro and treated with the carcinogen, methylcholanthrene, could be inhibited by vitamin A. More recently, Sporn et al. at the NCI showed that carcinogen-induced mouse bladder tumors could be largely prevented by feeding the animals 13-cis retinoic acid. Sporn's group also demonstrated that carcinogen-induced rat mammary tumors could be reduced to as low as one-fifth the expected incidence by feeding synthetic retinoids after carcinogen exposure. Boutwell and his colleagues at the University of Wisconsin have also shown that the administration of synthetic retinoids to mice inhibits the promotion stage of skin cancer induction. While these are but a few examples, laboratory data in general are consistent in various animal models and across animal species, indicating potential for human benefit. The chief aims of current laboratory research are to develop carcinogenesis inhibitors which have a strong protective effect, low toxicity, and which act on the late stages of promotion, as well as to understand how these inhibitors work.

Evidence from epidemiologic and laboratory research points to the role of certain micronutrients as inhibitors of various stages of the carcinogenesis process. In epidemiologic studies, persons eating diets high in various micronutrients have a lower incidence of certain cancers, especially breast, colon, and uterus. In animal studies the incidence of certain cancers, including skin, breast, and bladder, can be reduced by increased intake of certain micronutrients, such as retinoids.

In addition, dietary surveys have shown that smokers who have a high vitamin A intake (carrots, milk, and eggs) have a lower lung cancer risk than those consuming less. Rather extensive laboratory studies show that several rodent and murine skin, bladder, trachea and breast tumors can be prevented by various synthetic retinoids, including 13-cis retinoic acid, probably by control of epithelial differentiation. Human intervention studies now include: a pilot evaluation of beta-carotene among physicians; application of retinol in a gel form to the cervix to prevent the progression of dysplasia to cancer; use of vitamins C and E in patients with familial polyposis to determine

whether progression to colon cancer can be prevented; and use of 13-cis retinoic acid, an agent approved for acne treatment, to prevent development of new basal cell skin carcinomas in patients who have previously had these removed.

Rather limited case-control and correlation epidemiologic studies provide evidence that consumption of foods rich in vitamin C is associated with a lower risk for certain cancers, particularly gastric and esophageal cancers. Ascorbic acid, a water soluble antioxidant, can prevent chemically induced transformation of cells in culture.

Vitamin E (alpha-tocopherol) like vitamin C is an antioxidant which competes for available nitrites, thereby blocking the formation of carcinogenic nitrosos compounds. Unlike vitamin C, however, alpha-tocopherol is lipid soluble. There is limited, and sometimes conflicting evidence, that vitamin E may inhibit tumorigenesis in several model systems but there are no reports of its effect on nitrosamine-induced neoplasms. Clinical studies on vitamin C and E as potential chemopreventives have been initiated in patients with polyposis coli.

In the continuum which runs from basic research to application of research results to the population at large, the state of knowledge in this field requires additional human intervention trials as the next step. These trials will: confirm that animal model results are applicable to humans; clarify specificity which is imprecise in epidemiologic studies; evaluate toxicity and risk/benefit relationships; and, begin to evaluate the feasibility of applying a given intervention to the population at large.

A number of clinical studies of chemoprevention have been initiated, and others are being planned, to evaluate the long term use of potential chemopreventive agents in a controlled way. Attention must be given to factors including compliance, other extrinsic carcinogenic factors, and study end-points. Conduct of clinical trials is essential in order to address the question of safety and effectiveness of chemopreventive regimens in humans; the opportunity now exists to expand studies to new population groups to further delineate the range of tumor type for which chemopreventive agents may be effective.

● Nutrition

The objective of NCI nutrition research is to determine the role of dietary components in human health status in general, and on cancer development and progression, in particular. It is through this research that the development and evaluation of dietary modifications aimed at the reduction of cancer will take place. Included as part of this area are studies to elucidate the metabolic role of nutrients; the interaction of genetic-nutrient-environmental factors in disease etiology or progression; the influence of nutritional factors on disease treatment and patient recovery; the nutritional content of

various foods; and the effects on food of processing, retail practices, and other similar activities. Also included is the identification of determinants of dietary practices and methods of altering such practices in human populations.

As the the knowledge base regarding the role of nutritional factors in development and progression of cancer continues to expand, the opportunity exists to develop and evaluate dietary modifications which have the potential for preventing 35 percent of all human cancer (Doll and Peto). The expansion of knowledge regarding human nutrition and the identification of effective cancer preventive diets offers a cancer prevention approach which could be widely adopted by the general public.

Epidemiologic and laboratory studies provide strong evidence that dietary factors play a significant role in the incidence of cancer in humans as well as in the inhibition of one or more stages in carcinogenesis in animals. Both types of studies have shown a correlation between dietary fat intake and the incidence of cancer of the breast, colon, prostate, and endometrium. Laboratory studies have demonstrated that both saturated and unsaturated fats, from plant or animal sources, increase the incidence of breast and colon cancer.

With regard to dietary fiber, epidemiologic studies show an inverse correlation between fiber and the incidence of cancer of the breast and colon. In animal models, dietary fiber has been shown to reduce the incidence of colon cancer. Dietary fiber includes a range of chemical compounds that are not readily digestible in the human intestinal tract and may be divided into two broad classes of chemicals, complete polysaccharides and phenylpropane polymers. Polysaccharide fibers are fermented by colonic bacteria and lower pH in the large intestine which may alter the metabolism of carcinogens in the colon. Phenylpropane polymers are more resistant to digestion or fermentation and increase stool bulk. Their effect may be through either dilution of fecal carcinogens, or by absorption of carcinogens to polymers.

Long-term clinical trials are to be initiated in 1984 to evaluate the impact of a reduced level of dietary fat (e.g., a 20 percent fat diet) on the incidence of breast cancer in a population of women who are at high-risk for breast cancer. A second study will evaluate the impact of the low fat diet on the risk of recurrence of breast cancer in women who have been treated surgically for breast cancer. Still another trial is underway to evaluate the impact of dietary fiber on the progression of intestinal polyps to colonic cancer.

Epidemiologic and laboratory evidence is now converging toward the conclusion that some relatively simple dietary modifications may be able to have a significant impact on cancer incidence. The dietary fat intervention trials will provide evidence as to whether reduction in overall fat intake can reduce the incidence of breast cancer or its recurrence among women at high risk of disease. Continued support of the dietary fiber trial will elucidate the effect of fiber as a cancer-preventive agent.

Further research is needed to expand our base of information on the mechanism of action of the different fiber components and the distribution of these fiber components in different food groups. With this information, it would be possible to develop a dietary clinical trial with the goal of reducing the incidence of cancer of the breast, colon, prostate, and endometrium, through reduction in dietary fat and an increase in those fiber components anticipated to have the greatest impact on carcinogenesis. This group of cancers constitutes more than one-third of all cancers, and dietary manipulation which would reduce the incidence of these cancers would have a major impact on the overall cancer incidence in this country.

In addition, because eating habits are deeply engrained in most people, research is required to better understand the informational and behavioral strategies which may assist people in changing their diets in the recommended directions.

- Smoking, Tobacco, and Cancer Program Prevention and Cessation of Tobacco Use

Fifty-four million Americans--one in every three adults--smoke cigarettes regularly. Over 6 million teenagers smoke on a daily basis. More than 100,000 pre-teenagers are habitual smokers. Nearly 4,000 youth begin smoking every day. At the same time, the Surgeon General has identified cigarette smoking as the major single cause of cancer mortality in the U.S.--over 130,000 Americans will die of cancer this year because of the higher overall cancer death rates that exist among smokers as compared with non-smokers. Further, lung cancer rates among males have increased 175 percent, and over 250 percent among females since 1955. Smokers who consume two or more packs of cigarettes daily have lung cancer mortality rates 15 to 25 times greater than non-smokers, and associations have been identified between cigarette smoking and laryngeal, oral, esophageal, bladder, kidney, pancreatic, and stomach cancers. The Surgeon General, Dr. Koop, has stated that "Cigarette smoking is the chief, single, avoidable cause of death in our society and the most important public health issue of our time."

A wide range of actions are possible to reduce cancer mortality due to cigarette smoking by the year 2000 and beyond. A number of intervention techniques aimed at the prevention and cessation of tobacco use have been tested on a relatively small scale and appear to offer some measure of success. The opportunity now exists to field-test the more promising of these approaches (e.g., use of physicians and dentists to assist patients in stopping smoking; self-help strategies; mass media techniques; and programs aimed at school-based populations) on a large scale.

There are several reasons why this is a particularly opportune time to act on smoking prevention and cessation. First, results of the smaller scale studies mentioned above provide a foundation for testing and applying smoking prevention/cessation interventions on a larger scale. Studies in England suggest that brief, structured

interventions by physicians could have a major impact on smoking prevalence if large numbers of primary care physicians instituted such practices. Mechanisms in the self-quitting process also have been identified which, if made available to smokers in an appropriate form, could have a significant effect since the majority of smokers do quit on their own. Several limited mass media studies have indicated that the media may be the most valuable of the prevention/cessation approaches but the techniques used in these studies require broader application. A number of school-based prevention approaches also have been developed which have produced positive results with limited audiences and now require testing on a broader scale.

Second, since high interest in prevention/cessation related tobacco studies is relatively new, this field has only now begun to produce the numbers of trained researchers needed to mount a major research effort.

Finally, there is reason to believe that public awareness of tobacco and health issues may have peaked, and renewed efforts to stimulate this awareness and promote prevention and cessation activities are required. Ambiguous information on the effects of sidestream smoke, smokeless tobacco, and low tar/low nicotine cigarettes have all served to present the public with an equally ambiguous view of the health effects of tobacco use. Continued epidemiological monitoring is needed to provide more accurate information and refocusing of public awareness.

As noted above, recent Surgeon General's Reports have identified cigarette smoking as the single most important environmental factor contributing to premature mortality in the United States. Further, these reports conclude that cigarette smoking is the major single cause of cancer mortality in the United States, contributing an estimated 30 percent of all cancer deaths. The most desirable approach to reducing tobacco-related cancer is to eliminate, prevent, or reduce habitual cigarette smoking.

Several reasons exist in support of according high priority to research on smoking cessation/prevention--availability of new techniques for cessation/prevention; existence, for the first time, of a solid core of qualified research personnel; and, ambiguous public knowledge of the topic. Among other more specific rationale are the facts that lung cancer will supplant breast cancer as the leading site for cancer mortality among women, requiring immediate attention to be given to smoking cessation/prevention in this group; rates of tobacco-related cancers among Blacks now exceed those of Whites and rates among Hispanics are expected to follow the pattern among Blacks, requiring immediate action if these trends are to be reversed; and, the widespread introduction of nicotine chewing gum during 1984 will require monitoring both as to its effects and the possibility that it may give false impressions concerning either the difficulty of smoking cessation or the health effects of tobacco use.

- SEER

The Surveillance, Epidemiology and End Results (SEER) Program, consisting of a group of eleven population-based cancer registries covering about 12 percent of the U.S. population, provides a basis for assessing changes over time in cancer incidence, mortality and patient survival and differences in these measures among various population sub-groups. This system also serves as a mechanism for conducting large-scale epidemiologic studies to test specific hypotheses concerning possible etiologic agents.

Several unique opportunities are provided through the SEER Program. The Program began in 1973 and, now that sufficient time has elapsed for followup, patient survival data were published for the first time in 1982. Survival data continue to be analyzed in detail, taking into account the extent of disease at diagnosis, tumor cell type, and method of treatment. These analyses will provide information on a large scale on current results of cancer treatment and will be carried out annually to provide an ongoing assessment of improvement in cancer treatment.

SEER data also have been used for a number of large epidemiologic case-control studies in an attempt to identify factors associated with increased risk of cancer. For example, a study completed two years ago assessed the relationship between artificial sweeteners and bladder cancer. A large study is underway to evaluate the possible role of oral contraceptives in increased risk of breast, endometrial and ovarian cancer. Further studies are planned for 1985.

With regard to cancer control activities, the SEER Program provides data essential for the identification and study of areas, or population groups, with unusual cancer profiles. At present, SEER incidence, mortality and survival data are being utilized to identify areas that are most likely to be in need of cancer control intervention and to then monitor the impact of such intervention following its implementation. Such areas might be characterized, for example, by excessively high cancer mortality in comparison with the incidence present in that area. In addition, further research is planned to determine how to extend the SEER methodology to areas not covered by the program. For example, it may be possible to estimate cancer incidence through demographically-based functions derived in SEER areas and projected to non-SEER areas and supplemented by population-based surveys.

The SEER Program is critical as a device for monitoring progress of the National Cancer Program. For example, the effect of reduction in smoking among some of the male population is slowly becoming evident--the SEER data reveal a decrease in the rate of increase of male lung cancer incidence. The overall 5-year relative survival rate for those diagnosed from 1973 to 1980 is 48 percent; although earlier survival data are not strictly comparable, a similar figure for the period 1967-1973 was 41 percent. The SEER data also have shown striking changes in survival rates in cancers for which treatment

breakthroughs have been achieved; for example, among children diagnosed with acute lymphocytic leukemia between 1973 and 1980, the 5-year relative survival rate was 58 percent, while the corresponding figure for those diagnosed during 1960-1963 was only 4 percent. Similarly, there was a dramatic improvement in survival among those with advanced nonseminomatous testicular cancer in the 1970's. Those diagnosed during 1976-1978 experienced a 30-month survival rate, which is 2 1/2 times the rate experienced by those diagnosed during 1973-1975. Thus, SEER data make it possible to monitor, on an ongoing basis, the impact of advances in the management of cancer. The Program is crucial to the cancer control program for setting national objectives aimed at reducing cancer mortality and for monitoring progress toward achieving these goals. Because the SEER Program serves as the descriptive underpinning for a strong cancer epidemiology program and provides a basis for monitoring progress across a number of institute programs, this area of research is given high priority.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

I. Major Program Changes, FY 1986

● Research for Mothers and Children

In the area of Clinical Nutrition and Early Development, there will be: (1) a progressive expansion of the new initiative on low birth weight and high risk pregnancy; (2) new studies on the biological effects and long term safety of the use of ultrasound during pregnancy; (3) establishment of networks of maternal-fetal medicine units and neonatal intensive care units to examine therapeutic modalities in pregnancy and the neonatal period; (4) experimental and clinical studies on the nutritional requirements of newborns and infants and appropriate nutritional therapy for high risk prematures; (5) several new investigations of subgroups of children with Sudden Infant Death Syndrome as classified by differences in certain pathological findings; and (6) evaluation of the effects of obstetrical management on the course and outcome of pregnancy.

In the area of Mental Retardation and Developmental Disabilities, there will be: (1) an expansion of the research program on genetic and environmental causes of mental retardation; (2) a new initiative on research concerned with the impact of mental retardation and developmental disabilities on families; (3) an initiative to develop improved methods of early diagnosis and assessment for infants born at risk for mental retardation and developmental disabilities; and, (4) emphasis on the problem of dual diagnosis, a problem in which the client is both mentally retarded and mentally ill.

In the area of Human Learning and Behavior, there will be a major initiative in behavioral pediatrics. This will include: (1) expanded research on the genetic, neurobehavioral and behavioral factors which underpin subtypes of dyslexia, (2) new studies on factors involved in risk-taking behaviors and accident prevention in children, (3) research on compliance with medical regimens by acutely and chronically ill children, (4) research on behavioral factors involved in eating disorders and obesity, and (5) research on psychoneuroimmunology involving the relationship of behavioral factors to immune competence and health.

● Population Research

In Basic Biomedical Research, there will be expanded studies of (1) reproductive immunology, in view of the increasing evidence that immunologic factors play crucial roles in reproductive processes; (2) the treatment of infertility and of various diseases of the reproductive system; and (3) neural and endocrine influences on reproductive processes.

In Contraceptive Development, research on specific immunological approaches to contraception will be expanded in an effort to discover new immunogens and to improve methods for their production. Issues such as the safety and efficacy of potential vaccines will be carefully studied. Clinical trials will be initiated involving improved barrier methods and the most promising dosing regimens of LHRH analogs. Research on natural family planning will be expanded in an effort to improve identification of the beginning of the preovulatory fertile period, and clinical trials will be initiated to assess the efficacy of the techniques developed.

Studies of the safety of contraceptive methods will be expanded by (1) reevaluating the risk of cardiovascular disease for oral contraceptive formulations of the 1980s; (2) evaluating the metabolic activities and potencies of different components of oral contraceptives; and (3) evaluating the effects of possible interactions between the use of oral contraceptives and estrogens or estrogens with progestogen in menopause.

In the Demographic and Behavioral Sciences, there will be expanded studies of the effects of child care and employment on fertility; use of contraceptive techniques and sterilization; family and household structure; and the influence of perceived costs on childbearing decisions. In addition, studies will be initiated on fertility-related behavior of young men, childbearing patterns of immigrant groups, and methodological developments in fertility research.

● Intramural Research

The Cell Biology and Metabolism Branch will begin a major initiative directed toward clarifying developmental aspects of intracellular structure and function. Various methods will be utilized to study receptor biosynthesis, dynamics, regulation and degradation, using the human transferrin receptor as a model. The branch will also conduct clinical research on the fundamental mechanisms and treatment of patients with genetic disorders of iron metabolism to learn how the intracellular traffic of iron is normally controlled. The new initiative will reflect one of the few attempts nationwide to study the developmental aspects of nutrition and metabolism with the tools of modern cell biology. Iron-deficiency anemia remains the most common nutritional problem in the U.S. and throughout the world.

The Laboratory of Comparative Ethology will embark on a major study of the development of behavior in primates and other animal models. The interactions of genetic and environmental factors with behavior will be explored using a comparative mammalian approach so as to determine the origins and evolution of various behavioral phenotypes. This represents a unique attempt to correlate experimental results in primates with the results of longitudinal studies in human infants and families.

In the Laboratory of Theoretical and Physical Biology, a major initiative will be the development of a facility for graphic three-dimensional imaging of intracellular and intra-tissue structures, using powerful new computer-modeling techniques. Full-color, three-dimensional stereo images will be created using two-dimensional data input (e.g., electron microscopic serial sections through a tissue) thus revealing functional and topographic relationships not previously known. This Laboratory will also undertake a significant modernization of its mass spectrometry facility, permitting an expansion of its research activities.

In the Laboratory of Molecular Genetics, a major expansion will occur in the study of mammalian gene transfer. Previous results in this and other laboratories suggest that genes can be transferred into mammalian germ cells and be stably integrated and expressed. An intensive scaling up of the mouse model is a prelude to human gene therapy.

II. Areas of Scientific Opportunity

● Low Birth Weight Prevention

●● Fetal Growth Factors

A number of substances have been identified that act on various aspects of growth. These substances include nerve growth factor, growth hormone, epidermal growth factor, somatomedin C1 and 2, prolactin, and platelet derived growth factor. Virtually nothing is known about how these substances affect growth of the fetus, and their possible role in IUGR. With new immunologic techniques it is possible to develop antibodies specific for each of these growth factors, administer the antibody in pregnancy, and assess the effect on fetal growth.

It is important to determine what role, if any, these little-studied substances play in normal fetal growth and IUGR.

●● Biological Predictors of Fetal Growth

A number of biological measurements have been suggested, but inadequately assessed, as predictors of probability of delivering a low birthweight infant. Among these the most promising is measure of maternal plasma volume. Normally plasma volume expands by 9 weeks gestation, with expansion reaching a maximum at 24-26 weeks gestation. Failure of this volume expansion to occur is associated with a high incidence of LBW due to IUGR, and often with pre-eclampsia. Careful assessment of plasma volume change in pregnancy to evaluate this association is needed, using more precise measurement than hemodilution as reflected by hematocrit change. A new method for precisely assessing plasma volume by injecting red cells tagged with a stable isotope of chromium overcomes the potential hazard of radiation exposure during pregnancy, thus providing the means for a trial to assess this possibility.

Other potential predictors of IUGR, such as the ratio of plasma deoxycorticosterone to aldosterone levels, red cell sodium efflux, and salt retaining factors, are also worthy of study as possible predictors of LBW.

Present predictors of LBW rely on social, demographic, or historical factors and correlate only weakly with LBW. Availability of a biologic marker of higher reliability would facilitate early identification and intervention in a clearly high-risk population.

●● Biochemistry of Labor

NICHD scientists are coming closer to understanding the biochemical events that characterize normal labor, but the biochemical signal(s) that initiate labor remain elusive. Many of the animal models developed for study of this event have proved not to apply to the human situation. Micromasurement techniques are now being used to study initiation of labor in the human, searching for signals from the fetus, from stress, or from exogenous sources such as microorganisms that may be responsible.

Knowing the normal and abnormal initiators of labor would permit design of specific counter-measures to apply when labor begins too early.

● Normal and Abnormal Development

●● Involvement of Oncogenes in Development

Oncogenes are DNA sequences present in a virus which apparently derived at some point from normal cellular genes. These normal genes had somehow been picked up by viruses during the course of a previous infection, and now in subsequent infections can be re-introduced into a cell, where their expression is uncontrolled. The expression of the normal cellular genes has been shown to be tissue specific and stage specific in development in several cases. These genes also appear to have been highly conserved during evolution. Several retroviral oncogene, as well as cellular oncogene, products are now known to be protein kinases that catalyze phosphorylation of tyrosine residues on specific cellular proteins. Alteration of cellular metabolism by specific protein phosphorylation (often in response to surface receptor bound polypeptides is a well-documented phenomenon. Other cellular oncogene products appear to be DNS binding proteins that could affect activity of nuclear chromatin, similar to the action of certain steroid hormones.

Oncogene research, which is moving rapidly and has recently made significant contributions in the exploration of malignancies, also holds promise for new information on embryonic development. There is preliminary evidence suggesting that the normal cellular counterparts to oncogenes are important components of intercellular signaling systems during normal embryogenesis. The role of

oncogene products in normal development now needs to be examined by determining the patterns of oncogene expression during embryogenesis. Furthermore, the study of oncogenes also promises to elucidate the mechanisms of cellular aging and of cellular differentiation. These studies are proposed in various mammalian and non-mammalian systems. Abnormal functioning of these genes eventually may be found associated with birth defects, as already shown with neoplasia.

●● Fetal Physiology

Perinatal medicine has recently entered a new phase with the demonstration that certain fetal defects are treatable in utero. Such therapies have included both medical approaches, such as fetal cardiac digitalizations and surgical techniques, such as continuous drainage of hydronephrosis (dilated urinary excretory system) and hydrocephalus (accumulation of cerebrospinal fluid in a dilated ventricular system).

Identification of fetal patients who are optimal candidates for prenatal interventions has been difficult because of limitations of diagnostic capability, and because of the limited state of knowledge of fetal physiology and patho-physiology. However, both limitations appear amenable to research efforts. For example, the emerging technique of chorionic villus sampling (CVS) offers the potential of earlier diagnosis of genetic and metabolic abnormalities. Improved fetal therapy will require better knowledge of pharmacology in the fetus, so that drug therapies can be effective and safe. Prenatal interventions must also be evaluated from a behavioral standpoint, for which animal models may also be appropriate.

Clinical perinatal practice is moving rapidly toward fetal therapy as a means of improving over the results of intervention for abnormalities initiated in the newborn. Many physiological differences exist between fetuses and newborns. Considerable basic research will be required to determine the types of fetal therapy which are truly advantageous, and from which fetuses will benefit the most. Simultaneously, certain interventions will be found to be more appropriate in the newborn infant. This knowledge will conduce to better care during the perinatal period.

●● Safety of Chorion Biopsy

A new method of prenatal diagnosis has recently been developed which can be implemented during the first trimester of pregnancy. Called chorion villus sampling (CVS), the procedure involves aspirating small fragments of tissue from the developing placenta through a catheter, which is introduced through the cervix under ultrasound guidance. CVS holds great promise for making diagnoses of fetal abnormalities very early in pregnancy and is expected to come into widespread use in the United States. However, the safety of the procedure for the mother and the fetus

has not yet been adequately assessed. Further, it is not yet known whether the procedure is as accurate as amniocentesis which is currently the standard method of making prenatal diagnoses.

It is generally anticipated that this procedure will come into widespread use in the United States over the next few years, largely replacing amniocentesis. Consequently, there will be a limited time period during which both procedures will be in use in large numbers of women. This will create an opportunity to compare the accuracy and safety of the two procedures and to document this information for the benefit of physicians and patients in the future.

Since experts in the field agree that CVS will come into widespread use, it is clearly important to document the risks which are associated with this new technology. Furthermore, reported mosaicism in chorionic tissue suggests the need for a careful assessment of accuracy.

- Behavioral Sciences and Mental Retardation

- Identification of Infants at Risk for Mental Retardation and Developmental Disabilities

The ability of newborns who are born prematurely or with medical complications to survive has improved in the last several years. The major contributor for the increased survival rate is the great advances in neonatal medicine. Nevertheless, it is estimated that about one-third of these babies will have some major handicapping condition which will limit the quality of life and threaten their normal development. In most cases, these handicaps will not be discovered until the second or third year of life. Early educational and behavioral intervention may ameliorate the handicapping conditions. However, one barrier to beginning intervention early enough is identifying which infants are at risk for handicap.

Basic research in infant behavior has led to the development of new techniques for understanding normal and abnormal development in infants. These methods could be developed as screening tools and be used to follow the infants who come out of Neonatal Intensive Care Units in order to identify those infants who are at risk for developing handicapping conditions. Present methods are not sufficiently detailed to suggest effective interventions. The new techniques provide extremely detailed information which suggests specific intervention strategies.

Behavioral markers of developmental disabilities and mental retardation are capable of detecting early subtle signs of handicapping conditions. The recent advances in infant behavioral research, coupled with advancing computer technology, will allow earlier and more detailed identification than has been possible to this point. Prospective longitudinal investigations of

infants whose biological condition has been stabilized will permit the development of sophisticated screening devices. These techniques will contribute to the prevention of more serious handicaps through early identification and treatment of these conditions.

●● Biobehavioral Approaches to Subtyping Dyslexia

Dyslexia is characterized by a significant impairment in the development of reading skills which is not accounted for by chronological age, mental age, or inadequate schooling. Thus, dyslexia is a term which probably includes a wide variety of etiological factors, severity levels, and behavioral characteristics. The need to refine the definition of dyslexia has led to a search for distinct subtypes of dyslexia utilizing a variety of genetic methods. These efforts parallel the successful scientific strategy used to divide mental retardation into its many specific subtypes.

Recently, it has been demonstrated that a specific type of dyslexia can be attributed to a gene which shows an autosomal dominant mode of inheritance and is linked to a gene near the centromere in the long arm of chromosome 15. Studying the behavioral characteristics of the affected family members with this form of dyslexia has permitted behavioral scientists to describe more precisely the behavioral phenotype associated with this subtype of dyslexia. For example, this type of dyslexia shows no history of neurological deficits, no increase in left-handedness, no greater than expected number of hyperactive individuals, a "right-hemisphere" strategy for reading text oriented upside-down, slow oral reading with many errors, reading nonsense words differently than unaffected individuals, misspelling as a function of departure from spelling rules and regularities, and most make their spelling errors in the middle of the word. Since the most critical element for an effective genetic analysis of dyslexia is the rigorous definition of the phenotype, replicating the behavioral characteristics of the chromosome 15 linked dyslexia is an important step in establishing the validity of subtyping by genetic linkage methodologies.

In addition to behavioral assessments, the chromosome 15 linked form of dyslexia could be investigated for phenotypic homogeneity by utilizing new techniques developed in the past few years which assess neurological functioning of individuals during reading or reading-related activities which include refinement of EEG measures, computer assisted tomography (CAT scanner), positron emission tomography (PET scanner), nuclear magnetic resonance (NMR), evoked response techniques, and magnetoencephalograms. Integrating the behavioral and bio-behavioral measures of the individuals with the chromosome 15 linkage type of dyslexia will provide a greatly refined definition of the specific disabilities associated with this type of dyslexia.

The ability to analyze the dyslexias into different subtypes of several different genetic methods should allow behavioral scientists more homogeneous sample populations for testing the influences of environmental variables on the development of reading. A number of new techniques have been developed in recent years which add new dimensions to subtyping dyslexia. One advance has been to combine chromosomal banding techniques and linkage analysis to identify a genetic basis for the dyslexias. Improved chromosomal banding and restriction enzyme techniques will provide more precise descriptions of the location and function of genes associated with the dyslexias. Complex segregation analysis of nuclear families and pedigree analysis of complex family structures have been used to examine the mode of genetic transmission for a broad range of disorders, including stuttering and Gilles de la Tourette syndrome. These methods used in genetic epidemiology can be applied to the study of dyslexia to investigate the underlying genetic mechanisms. Although the prevention of dyslexia is in the distant future, the genetic analysis of dyslexia will provide a basis for establishing high risk populations which can be studied throughout their development for different behavioral characteristics. Differential teaching strategies for established sub-types of dyslexia which can target upon specific deficits may be possible to develop.

Estimates of the prevalence of dyslexia range from 1 percent to 15 percent. While the definition may be equivocal, the problems associated with individuals who are unable to read are legion. The cost in educating dyslexic individuals has increased significantly since the enactment of P.L. 94-142 with its requirements for appropriate individualized educational plans for all disabled children. In addition, approximately half of the nation's unemployed youth (aged 16-21) are functionally illiterate.

The NICHD has funded research on reading disability since the inception of the Institute. In the fiscal years 1977-79, NICHD sponsored approximately 76 percent of all United States sponsored research on dyslexia.

●● Comparative Behavioral Genetics

A new NICHD intramural research program has been initiated, in collaboration with the NIMH, on the genetics of behavioral development in a rhesus monkey model. These monkeys, which were bred over four generations by Harlow and Suomi at the university of Wisconsin and have not been moved by Suomi to our program, segregate into two behavioral phenotypes, "uptight" and "laid back." These behaviors are only manifested under stress, but are detectable shortly after birth and throughout life. "Uptight" monkeys, when stressed, display autism, learning and communication disorders, and addictive behavior. Mothers with this phenotype may abuse their infants, and animals of any age show poor "socializing" skills. Thus, this monkey model seems to display the full repertoire of normal and abnormal human behavioral

development. The monkeys have been raised within nuclear families, ie.g., a father, a mother and an infant, and several families are housed together in an apartment-like setting. Thus, families and social settings which approximate the human condition have also been replicated in this model. Heretofore, it has not been possible to exploit the model other than phenotypically; here, however, we can study genetic and environmental determinants of behavioral development at a more sophisticated level, including that of gene structure and expression. Moreover, infant monkeys of one behavioral genotype can be cross-fostered by parents of the opposite genotype; other variations on this theme provide us with an opportunity for determining whether the expression of behavioral genotypes can be prevented or treated through environmental maneuvers.

The rhesus monkey model will provide intramural scientists with an extraordinary opportunity to examine the important genetic and environmental events which condition normal and abnormal primate behavioral development, without the technical and ethical constraints imposed by analogous studies in humans. Moreover, this model is now in its fourth generation, with daily behavioral observations on all colony members having been accumulated for almost 20 years (as well as serial genetic and physiologic studies). The model is of highest priority not only to NICHD but to NIMH as well since it permits a window on the origins of normal behavioral development as well as psychopathologic states, learning and communication disorders, and addictive behaviors. The model is also of interest to NINCDS and NIAAA.

●● Developmental Neurobiology

NICHD neurobiologists have developed a tissue culture system which makes possible detailed correlations, during critical periods of neuronal development, between electrical activity, morphology, gene expression, peptide synthesis, and neural transmission. These correlations can be made in single cells. Moreover, this new in vitro system permits an assessment, at the molecular level, of the influence of drugs and toxins on subtle aspects of neuronal development. These workers have also developed computer models which permit facile analyses of complex, integrated neurobiologic phenomena. The biochemical and anatomic events which regulate synapse formation can also be identified in the in vitro system. This system of cultured neurons, with the techniques at hand, now provides an exceptional opportunity to illuminate the complex neurobiologic events responsible for normal and abnormal brain development. It is also possible to employ these techniques in studying experiential effects on neuronal organization, functional morphology, and chemical architectonics. Finally, even where markers are not available for specific human genes active in nervous system development, restriction fragment length polymorphisms (RFLPs) make possible a study of the entire human genome as it influences normal and abnormal CNS development.

The ability to analyze central nervous system development in vitro at the single cell and molecular genetic levels promises to revolutionize the study of the many types of mental retardation wherein no etiology has so far been identified. Prevention of mental retardation will also be facilitated through the use of the system and methods described herein, in that subtle environmental influences on the development of single neurons and synapse formation can now be established.

- LHRH Analogs--Agonists and Antagonists

- Development of LHRH Analogs as Potential Antifertility Agents for Both Men and Women

Preliminary clinical data do suggest that this group of drugs has the potential of being developed as contraceptive agents. Considerable research remains to be done in areas of synthesis, delivery systems, and clinical studies.

LHRH analogs represent a novel group of drugs. Although no definitive contraceptive regimens that are problem free have as yet been devised, the prospects are quite good for both the agonists and antagonists.

- Hypothalamic-Releasing Hormones: Agonists and Antagonists

The development of agonist and antagonist analogs of hypothalamic releasing hormones, especially GnRH, GRF, and CRF, has provided us with an opportunity to develop increasingly specific diagnostic and therapeutic approaches to such hormone-dependent disorders as endometriosis, polycystic ovaries, carcinoma of the breast and prostate, precocious puberty, acromegaly, dwarfism, and Cushing's syndrome. Moreover, GnRH analogues offer the potential for more effective and safe contraception as well as therapy for infertility. GnRH analogues have recently been synthesized which are effective orally. Clinical trials of such agents in this program have already shown a remarkable therapeutic result, particularly in the case of precocious puberty.

The ability to suppress or augment hormonally-mediated events with synthetic agonists or antagonists has already been used with excellent results in patients with endometriosis, polycystic ovarian disease, breast cancer, prostate cancer, and precocious puberty. Also, with proper pulsatile injection of GnRH, single ovulations can be induced, making this the safest agent for induction of ovulation in treating infertility. Similar regimens can be used to induce normal puberty in subjects with hypogonadotropic hypogonadism. There remains the great potential for these agents as a safe, effective contraceptive in men and women. With regard to disorders of growth and adrenal function, further development of the relevant analogues is also of high priority.

NATIONAL INSTITUTE OF DENTAL RESEARCH

I. Major Program Changes, FY 1986

The increase in research project grants, other research, contracts, and intramural research will permit the support of several new studies and centers as well as the growth of research in selected areas. The Dentist Scientist Award Program to be established in FY 1985 will be expanded. This program supports the integration of basic and clinical sciences in a program tailored to the needs of dentists at a time when there is a critical shortage of dentist-scientists. Increases for this program are reflected in both A. and B. below.

● Diseases of the Teeth and Supporting Tissues

These research areas include studies on the periodontal diseases, dental caries, soft tissue diseases and restorative materials. Examples of new and expanded research project grants include small-scale development of diagnostic methods to identify the "active" periodontal lesion; development of new chemotherapeutic agents for the prevention of periodontal diseases; research to characterize bone metabolism, microbiology, inflammation and immune responses involved in periodontal diseases; studies of the etiology and pathogenesis of tooth root caries; and studies of the biocompatibility of metals used in dentistry.

The increase in contracts would permit further expansion of a planned international collaborative epidemiologic study to investigate the causes for the decline in caries prevalence seen in several Western countries and the study of the relationship of periodontal diseases to both oral and other chronic diseases. Also, clinical trials such as a large-scale study of the use of slow-release fluoride therapy in caries prevention; the effect of a low-concentration fluoride dentifrice on caries in children; and a Phase I field trial of an anti-caries vaccine will be possible.

● Disorders of Structure, Function and Behavior

Research areas in this category include investigations of craniofacial anomalies, behavioral sciences and pain research. Types of research project grants include the development of improved procedures for craniofacial reconstruction; studies of wound healing; research on improved methods of diagnosis of craniofacial anomalies as well as improved methods to analyze treatment results; the isolation and characterization of enamel genes; studies of craniofacial morphogenesis to elucidate the role of muscles and respiratory function on dentofacial growth and deformities; the development of behavioral interventions for improved utilization of dental services; the study

of the natural history of temporomandibular joint disorders; and the study of orofacial motor function and dysfunction. In addition, research will continue on the adoption, diffusion and implementation of preventive technologies; on the prevention and treatment of dental fear and anxiety; and on the nature of dentist-patient interactions which reinforce preventive oral health behaviors.

The increase in contract funds will permit epidemiologic studies such as one to determine the incidence, characteristics, causes, age relationships, and natural history of acquired craniofacial defects.

- Dental Research Centers

In accordance with recommendations by the National Advisory Dental Research Council, the NIDR will begin reducing funding for the five noncategorical Dental Research Institutes in order to initiate a new program of specialized centers. Like the three Periodontal Research Centers, increased funding for these specialized centers will be displayed within A. and B. above. Two centers for the study of cariology will be initiated in FY 1984. In FY 1985 one or two research centers each will be initiated for the periodontal diseases and for behavioral studies. In FY 1986 the five centers to be initiated include orofacial pain and related disorders, oral ecology, geriatric oral health, oral mucosal diseases and dental biomaterials.

- Intramural Research

The expansion in intramural research will permit further emphasis on fluoride studies focusing upon toxicology and systemic effects; saliva and salivary gland research; investigations of the interactions of metastatic and nonmetastatic tumor cells with extracellular macromolecules; studies of the biochemical basis of latency of the Herpes simplex virus (HSV); development of a vaccine against HSV; clinical studies of acute and chronic pain; and research on basic mechanisms of pain transmission and modulation. In addition, research will be expanded on factors regulating bone cell activity; on the function, production and regulation of bone-specific proteins such as osteonectin; on studies to assess the role of the herpes virus in human neoplasia; and on investigations of host factors implicated in chronic inflammatory tissue destruction.

II. Areas of Scientific Opportunity

- Epidemiology of Oral Diseases and Conditions

Epidemiologic data on several oral diseases and conditions are critically needed as a basis for determining the extent and magnitude of dental problems as well as for research planning purposes. Some data need to be updated. The incidence and prevalence of other emerging diseases and conditions need to be assessed for the first time on a national level. Dental caries of the tooth roots is such a disease. As more teeth are retained, root surface caries is expected to become

an increasingly serious public health problem. Data collected in local geographic areas suggest that national distribution patterns might be of prime importance. The relationship of root caries to enamel surface caries as well as to demographic and geographic factors should also be examined.

The NIDR 1979-1980 National Dental Caries Prevalence Survey showed a marked decrease in caries prevalence in children 5-17 years of age compared with a previous National Center for Health Statistics survey. A smaller decrease in caries prevalence apparently has been experienced by the older aged children studied. The 1979-1980 baseline survey should be followed up in FY 1985 to observe disease patterns in school aged children. In addition, there is a need for a caries prevalence survey of adults.

The prevalence of periodontal diseases in the U.S. population is not known with any degree of confidence. As a result of the increase in older segments of our population and declines in tooth loss because of widespread use of caries-preventive measures, it is expected that diseases of the periodontal tissues are growing in importance. Well-designed and implemented studies to determine the incidence and prevalence of these diseases are in order. In addition, information on the relationship of periodontal diseases to both oral and other chronic diseases, such as rheumatoid arthritis, is needed.

Information regarding incidence, characteristics, causes, age relationships, and natural history of acquired craniofacial defects, including follow-up studies of treatment outcomes is needed. In particular the number of patients who experience speech, voice and other functional disorders, and the type and effectiveness of the therapeutic services they are receiving, are needed.

Epidemiologic studies such as those mentioned above will take advantage of existing indices and survey methods, but others will require the development of new indices. Reprogramming of contracts permits the initiation of a national oral disease prevalence survey in adults in FY 1984 which would examine root and coronal surface caries and periodontal diseases.

The critical need for epidemiologic studies has been emphasized by all NIDR major program evaluations to date (Evaluation of the NIDR Periodontal Diseases Research Activity, 1976; Evaluation of the NIDR National Caries Program, 1979; Evaluation of the NIDR Craniofacial Anomalies Research Activity, 1981); by the authors and reviewers of state-of-the-science papers developed for the FY 1985-89 NIDR Long-Range Research Plan; by members of the NIDR Programs Advisory Committee; and by the dental literature. Monitoring the incidence and prevalence of oral diseases and conditions is essential to the evaluation and planning of research activities, as well as to the provision of adequate resources for care.

In the case of periodontal diseases and dental caries such data would update previous findings and reveal the impact of current preventive and therapeutic practices. With root caries, acquired craniofacial defects and certain other soft tissue pathologies there are no definitive data, and epidemiologic studies are essential to define the magnitude of the health problem to which research efforts are being addressed. Relationships of oral diseases and conditions with other diseases and with behavioral, social, cultural, and economic factors need to be elucidated in order to refine appropriate research questions and to facilitate progress towards disease prevention and treatment.

The cost of epidemiologic studies has been a deterrent in the past. Now, however, the need for data from these studies is so great that measures must be taken to carry out the necessary research.

● Dental Caries Prevention

Work toward an anticaries vaccine continues. Important questions to be answered include the immunogenic materials to be included in a vaccine, the most effective method of administration, whether adjuvants can enhance immunogenicity and the best age for vaccination. A plan has been developed for a clinical trial which should determine the feasibility of intragastric immunization with whole cells of Streptococcus mutans. Also studies of certain adjuvants as aids in stimulating the secretory immune response of intestinal lymphoid tissues appear promising.

More remains to be learned about the benefits of fluoride, its mechanisms of action, and delivery systems for its use. Intra-oral fluoride slow-release devices currently are being tested for performance, durability and acceptability in a small-scale short-term clinical trial in children. If the devices prove acceptable under these parameters, testing for effectiveness in preventing caries could commence in 1986 in a full-scale clinical trial. This trial would depend upon the availability of a sufficient number of devices.

Root caries remains an area of scientific opportunity. At present a clinical trial is under way to examine the effects of fluoride mouth-rinsing on root caries. Basic research studies are also needed to identify the microorganisms responsible, to clarify mechanisms of microbial colonization, and to elucidate mechanisms leading to tooth root destruction. In FY 1984 a survey to determine the prevalence of caries in the cementum (root) surface of the teeth in working adults and the elderly in America, together with coronal caries and periodontal diseases will be initiated.

Dental caries remains a major oral health problem in the United States. If this disease is to be prevented, the needs of special target populations should be addressed, tooth site-specific caries must be better understood, and appropriate preventive programs encouraged.

● Research on Periodontal Diseases

Opportunities continue to exist in microbiology and specificity, in host response mechanisms, in diagnosis and in prevention of periodontal diseases. Bacteroides intermedius has been associated with suppurating pockets in adult periodontitis cases, adding to the growing body of evidence that different forms of periodontal diseases may be caused by specific bacteria. Actinobacillus actinomycetemcomitans has been associated with localized juvenile periodontitis and Bacteroides gingivalis with adult periodontitis. A firmer base for this bacterial specificity needs to be established.

Preliminary experiments have shown that specific antibodies against fimbriae of Actinomyces viscosus inhibit attachment of those organisms to tooth surfaces. Investigations indicating the production of lymphocyte-inhibiting substances by several periodontopathic organisms and studies demonstrating bacterial invasion into periodontal tissues have demonstrated the intricacies of the host response mechanisms involved in periodontal diseases. The dual role of the host's immunological system as both a protector and a possible source of destruction needs clarification. Host factors implicated in chronic inflammatory tissue destruction include proteases, antiproteases, prostaglandins, complement components, reactive oxygen species and lymphokines.

Accurate, rapid and objective methods of detecting and measuring the severity of the periodontal diseases--particularly the "active" lesion--are needed to evaluate disease status and the effect of treatment procedures. Emphasis will be placed on the development of such diagnostic systems as radioactive iodine absorptiometry, radiographic subtraction and tomosynthesis, and biochemical markers. Use of iodine absorptiometry has been demonstrated for the study of alveolar bone mass changes in periodontal diseases. These systems show promise for early detection of active disease as well as for measurement of disease progression.

Clinical studies of chemotherapeutic agents for the prevention of periodontal diseases are ready for implementation. Scientific evidence exists that some correlates of periodontal diseases are reversible and that other correlates may be prevented from development through chemotherapy. At a time when mechanical plaque removal is the most common approach to periodontal disease prevention, developing new chemotherapeutic agents and testing the efficacy of existing ones will augment the preventive armamentarium.

In addition to the above scientific opportunities, there is now evidence to indicate that the therapeutic value of tetracycline includes direct inhibition of tissue collagenase activity, expanding beyond the antibacterial properties of this drug. Further elucidation of the mechanisms of action and research on appropriate use of tetracycline in periodontal disease treatment are warranted.

Increased understanding of the etiology and host response mechanisms in periodontal diseases should expedite the development of diagnostic and preventive measures. Given the endemic nature of gingivitis and periodontitis improved control and eventual eradication of these diseases would substantially benefit the public's oral health.

● Dentist Scientist Development

The NIDR Long-Range Research Plan discusses in detail the past developments, current status, and future challenges in dental research. Impressive advances have been made in fundamental knowledge of oral diseases and the population has already realized significant oral health benefits. Work must continue not only at the basic science level but increasing attention must also be given to capitalizing on this knowledge and carrying the research through the logical steps that lead to clinical studies, trials, and applications to dental practice and disease prevention.

Essential to carrying out this research agenda is ensuring the future availability of the required number of dental investigators with appropriate skills. However, an analysis of the current supply and future requirements for dental research personnel and a review of the significant changes that have occurred in Government-supported dental research manpower development activities have focused attention on the critical need for dentist scientists. While there appears to be a general understanding within the research community of the issues associated with the shortage of physician scientists, the problems in dental medicine are even more acute. This is in part due to the fundamental difference between the professions in the structure and financing of their professional and graduate education programs. Even with the maximum utilization of currently available research training support programs, it is far more difficult for a dentist than a physician to prepare for a career as a clinical scientist.

It is imperative that action be taken to reverse the alarming decline in the number of dentists undertaking the comprehensive preparation needed for careers as independent dental clinical investigators. Such action must not, however, result in any diminution of the supply of basic scientists preparing for careers in dental research.

In order to address future scientific opportunities, a two-fold strategy is indicated. First, a new dental research manpower development program carefully designed to address current problems in preparing dentist scientists should be implemented. Such a program would parallel closely the new NIH Physician Scientist Award program but would be structured to the dental situation. It would mandate that the grantee institution integrate the basic and clinical science development program components with an intensive supervised research experience. Second, a concerted effort needs to be made to increase the stipend levels and increase the number of NRSA short-term training grants made to dental schools. Currently only one quarter of the dental schools have such programs. The purpose of this initiative is

to increase substantially the exposure of dental students to the challenging career opportunities in dental research and thereby increase the number of graduates electing such careers.

It is the judgment of the NIDR that the future of dental research is threatened by the ever-increasing shortage of dentist scientists. These individuals are essential in expanding knowledge at both the basic and clinical levels and, perhaps even more importantly, in bridging the gap between basic and clinical research. These conclusions are supported by the National Advisory Dental Research Council and other NIDR advisory bodies as well as the major dental professional organizations representing the dental research, education, and practice communities. A noteworthy example of the latter is found in the recently completed report of the Committee on the Future of Dentistry of the American Dental Association. Of the five most critical issues identified by an organization concerned primarily with the dental practice sector was one concerning dental research recommending that the NIDR renew efforts to train clinical investigators.

While the NIDR has undertaken its own assessment of the problems related to the preparation of dentist scientists and the adequacy of its training support programs, it should be noted that the National Academy of Sciences (NAS) has also recognized that a problem exists and has initiated a special study to examine the issues in dentistry. The NAS Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel called attention to the special problems and unique research training support needs in dentistry.

- Opportunities in Fundamental Biologic Research

Advances in research coupled with the availability of sophisticated new scientific technologies offer unique opportunities for progress in a wide range of areas including craniofacial development, salivary function, bone biology, tumor metastasis and wound healing.

Recent work has identified specific factors in the embryonic environment including a number of extracellular macromolecules such as collagens, fibronectin, laminin, other glycoproteins and glycosaminoglycans which appear to regulate cell migration, proliferation, and differentiation. With the identification and purification of these molecules it is now possible to study the specific interactions involved in the migration and differentiation of the cranial neural crest cells that lead to the formation of a variety of tissues in the facial region, including cartilage, bone, connective tissue, and much of the peripheral nervous system.

Saliva is of critical importance in the maintenance of normal oral and dental health. Many of the oral health problems of older adults appear to be the result of either specific age-related alterations in salivary gland function, especially prevalent in women, or changes secondary to disease and therapeutic treatments (e.g., pharmacologic,

radiologic) common to the elderly. Salivary function is also severely affected in patients with cystic fibrosis. Considerable progress has been made in understanding how the autonomic nervous system controls the function of the salivary glands. One important insight has been gained by the demonstration that oligosaccharide additions to salivary proteins can be modulated by neurotransmitter regulation. Since the oligosaccharide portion typically represents the critically important functional unit of biological activity, this finding suggests a mechanism by which drugs or diseases affecting neurohormonal control may alter the biological properties of saliva. This knowledge should facilitate the design of better therapeutic regimens to prevent or treat malfunctions of these glands. Furthermore, salivary glands are widely accepted as a useful model for studying exocrine secretory events. As a result, these studies have broad implications for understanding secretory physiology and diseases affecting other tissues.

Within the broad area of mineralization research major advances have been made toward elucidating the role bone cells and their secretory products play in normal growth and development and in diseases of bone. Prostaglandins, calcium ions, and cyclic nucleotides have been shown to regulate bone cell activity. Changes in electric potential in bone in response to physical force and specific immune factors can activate these regulatory systems. Several noncollagenous bone-specific matrix proteins have been identified. One of these, osteonectin, appears to be essential to normal mineralization, while others may regulate bone resorption or couple bone resorption to bone formation. Research into the function, production, and regulation of these bone-specific proteins provides opportunities for elucidating of basic processes involved in bone formation and bone turnover as well as an understanding of pathological processes. As an example, progress is being made toward understanding the underlying causes of osteogenesis imperfecta, a genetic disease of bone often called "brittle bone disease" that affects one out of 30,000 children born world-wide. Work with a new animal model of the disease in Holstein cattle has implicated impaired bone (and dentin) cell development, maturation and/or growth as the principal genetic defect responsible for the observed skeletal abnormalities in the disease. This suggests new modalities of treatment for the syndrome, based on known systemic factors having beneficial effects on bone cell growth and development.

Studies of matrix proteins have also made it possible to investigate the interactions of metastatic and nonmetastatic tumor cells. Particular emphasis has been directed toward understanding the role of laminin molecules in promoting or inhibiting the adhesion of cells to basement membrane. A high affinity receptor for laminin has been identified on the surface of tumor cells and the number of these receptors has been shown to correlate with the metastatic potential of the tumor cell. Another area under investigation concerns the preferential migration of certain tumor cells to specific tissues.

An invasion assay chamber has been developed incorporating a synthetic basement membrane as a barrier between two chambers. Target tissue extracts are placed in the lower chamber and tumor cells in the upper chamber. Data obtained so far indicate that the invasive activity of various tumor cells depends not only on their ability to penetrate basement membranes, but also on their homing to tissue-specific factors. In addition, this invasion assay chamber offers the opportunity to examine drug effects on tumor cell attachment to basement membrane, degradation of the collagen barrier, and locomotion through the barrier.

Extracellular macromolecules have also been found to play a major role in wound healing, attracting specific cells to the wound area and inducing them to proliferate and secrete new extracellular substances which, in turn, attract other cells to the wound. There are, however, rate-limiting steps in wound healing, particularly in the penetration of cells into the wound and their proliferation. Purified growth factors and chemoattractants speed wound healing and when administered to wounds in diabetic animals restore healing to normal. Advances in understanding normal wound healing also provide a basis for studies on "excessive" wound healing as in fibrosis, and ultimately should make it possible to inhibit this aberrant response.

The accomplishments of basic science research have provided the underpinnings for advances and applied clinical research especially as they relate to caries and periodontal diseases. Further progress in these and other program areas, however, depends on the continuing pursuit of the scientific opportunities which exist in basic science. Understanding the basic chemical and molecular events which regulate and control normal development is fundamental to the attempt to identify the causes of congenital craniofacial anomalies and to develop preventive measures for these defects. Understanding the basic processes involved in the normal formation and turnover of bones and in salivary function, tumor metastasis and wound healing is critical to the development of improved diagnostic, treatment and disease-preventive measures of periodontal diseases, craniofacial anomalies, oral cancer and other oral tissue conditions.

● Craniofacial Anomalies Research

Opportunities exist within each of the areas of congenital craniofacial anomalies, acquired craniofacial defects and dentofacial malrelations. Of great importance are studies aimed at gaining a better understanding of the biochemical mechanisms that regulate the processes of migration, proliferation, and differentiation of embryonic neural crest cells; molecular biology studies to elucidate factors associated with bone formation and resorption; and investigations of the involvement of cAMP and prostaglandins in the synthesis of extracellular and cell-associated matrix components required for normal palate differentiation. Also warranted are human studies of cleft lip and palate using methods to clarify the interaction between genetic and environmental agents.

Increased emphasis will be given to the isolation and characterization of enamel genes; improved procedures for craniofacial reconstruction and wound healing; further research on control mechanisms in craniofacial morphogenesis, particularly the role of extracellular matrix macromolecules; and the study of the role of muscles and respiratory function on dentofacial growth and deformities.

To date, no detailed study has been conducted to investigate the long-term effects of facial injuries. It is proposed that at least five broad areas be studied: (1) the incidence, severity, distribution, and etiology of facial trauma; (2) the effects of osseous and soft tissue trauma on subsequent craniofacial growth and development in children; (3) the effects of facial trauma on speech production, oral-motor function, mastication and deglutition; (4) specific laboratory and clinical studies to investigate the role of certain biochemical parameters in wound healing; and (5) the psychological consequences of craniofacial disfigurement.

Research and training opportunities in malocclusion and dentofacial deformities also exist in the following areas: (1) etiology; (2) prevention/interception; (3) growth prediction and basic control mechanisms; (4) diagnosis and treatment; (5) psychosocial aspects of dentofacial deformity; (6) need for and effects of orthodontic treatment on oral and systemic health; (7) relationship of form and function in facial development; and (8) basic bone biology.

Studies of the effectiveness and mechanism of action of functional appliances in orthodontics and on the role of nasorespiratory function in the development of malocclusion and severe dentofacial deformity hold promise for progress.

Topping the list of congenital craniofacial malformations are cleft lip and cleft palate which affect one out of 600 white infants. The incidence is higher among Orientals, native Americans and Eskimos, and lower among blacks. Other defects include such conditions as defects in ossification, facial asymmetries, and dental anomalies.

It is not known what proportion of craniofacial injuries result in long-term or permanent disfigurement or loss of function. Similarly, data are sparse, or lacking entirely, on the sources of injuries, the nature of injuries, the kinds of medical treatment required, the costs of such treatment, and the psychosocial consequences of these injuries and defects to the patient and his or her family.

National Health Survey data indicated that about 29 percent of all 12-17 year olds have a malocclusion for which treatment is considered either highly desirable or mandatory. At the present time, these data indicate that about one million new orthodontic cases occur each year.

The research opportunities described should address these health problems and lead to better prevention, diagnosis and treatment methods.

● Herpes Simplex Virus (HSV) Type I Research

The NIDR supports and conducts research on HSV. Efforts have been directed at understanding the biochemical basis of latency and work has progressed in two major areas. First, it has been demonstrated that in latent infection in mice the viral genome does not persist in trigeminal ganglia neurons in a physical state similar to that found in free virus particles. Instead it appears to be either integrated into the neuronal DNA or genetically rearranged in a manner unknown for the virion particle. Standard recombinant DNA techniques have been used to clone and amplify viral genes, but this approach has been unsuccessful so far due to the very low concentration of viral genes present in ganglia. New cloning techniques that involve genetic as well as molecular recombination are currently being attempted. In a second major area of research in situ hybridization techniques have shown that a few viral genes are expressed into mRNA during latency. Future studies will aim to clone these mRNA molecules in order to determine which specific genes are being expressed.

Last year DNA sequences in the HSV genome were found to share regions of homology with human DNA sequences. Some of the human DNA sequences have now been identified. They are present in the upstream region of the oncogenes of human bladder carcinoma and human osteosarcoma, and may play a regulatory function in the expression of these oncogenes. Other regions of homology are found in the switch regions of immunoglobulins. These results suggest a number of possible molecular mechanisms to explore that might explain the potential role of HSV in neoplastic transformation. First, recombinant DNA molecules are being constructed that contain HSV fragments linked to an oncogene or to its normal homologue in order to determine their transforming potential. Second, molecular biological approaches will be used to determine whether HSV may be involved in the etiology and pathogenesis of oral cavity tumors and neurological diseases of unknown origin. These experiments may provide a means to assess the possible role of herpes viruses in human neoplasia.

Work on the development of a subunit vaccine against HSV continues. Recombinant DNA clones containing various regions in the gene coding for the viral B2 glycoprotein have been obtained and the genes inserted into a number of expression plasmids. Some of the clones gave only transient expression of the B2 protein. In order to understand the basis for this lack of success, the DNA nucleotide sequence at the beginning of the gene was determined. This turned out to be a translational termination codon 5' to the initiation sequence of the gene and may be responsible for the transient expression observed. These sequences are now being molecularly edited in order to achieve high levels of protein expression.

A second approach for developing an HSV vaccine was initiated this year. This involves the use of vaccinia virus as a vector, and is being carried out in collaboration with NIAID. The D glycoprotein of HSV is another of the major antigenic determinants of this virus.

The gene for this protein has been isolated and genetically engineered into vaccinia virus. This hybrid virus, containing both the HSV D glycoprotein gene and vaccinia DNA, expresses the D glycoprotein in infected tissue culture cells. Experiments are now under way to determine if animals immunized with this hybrid virus will develop immunity and be protected against HSV. In addition, plans are under way to insert the gene coding for the B glycoprotein of HSV into vaccinia with the hope that this protein will also be expressed by the hybrid virus. A vaccine that contains both the B and D glycoproteins of HSV would be highly desirable for immunization.

Experiments are now being planned to study the effect of antiviral agents, such as vidarabine phosphate (ARA-AMP) and acyclovir (ACV), on the treatment, prevention and recurrence of oral herpes. Phase II clinical trials of the use of iontophoresis for the application of antiherpetic agents have been impressive. Using ARA-AMP, five out of ten subjects were virus free after 24 hours and eight were virus free after 48 hours. ACV was less effective in producing negative cultures but healing time was considerably reduced by both drugs. There was also a decrease in lesion area and reduction of pain soon after treatment. Phase III (double blind) studies of labial and cutaneous herpes treatment by iontophoresis have been started.

It has been estimated by a study of antibodies to the Herpes simplex virus type 1 that at least one third of the world's population has been infected, and that infection is more common among lower socioeconomic groups. In a large proportion of these people the painful, unsightly blisters of cold sores are recurrent. The NIDR is continuing its efforts to prevent and treat the lesions and other problems arising from infections of HSV type 1. The need continues for a better understanding of how HSV interacts with the host, of the fundamental processes of replication and mechanisms of latency, and of human defense mechanisms, including various cellular and humoral responses.

● Research on Oro-facial Pain and Sensory-motor Dysfunctions

Important research opportunities to be pursued include studies of the temporomandibular joint (TMJ) disorders, mechanisms of acute and chronic pain, and oro-facial motor function and dysfunction. TMJ disorders appear to be quite common; however, there is a need for TMJ disorder indices and then epidemiologic studies to determine the true prevalence of this condition in the United States. Also essential are investigations of the etiology, pathogenesis, diagnosis, prevention and treatment of TMJ disorders. The development of standardized diagnostic criteria is essential. Use of recently developed digitized x-ray tomographic scans may aid diagnosis and provide a rationale for new treatments. A greater understanding of the role of behavioral variables in symptom development and treatment responsiveness is also important.

Clinical studies of acute and chronic pain and basic research on pain transmission and modulation continue to show significant progress. Emphasis in the clinical area is on multidisciplinary studies of pain assessment, pain mechanisms and treatment approaches. An average of 40 acute pain and 26 chronic pain patients per week are seen in the Ambulatory Care Research Facility (ACRF) Pain Research Program Clinic. Present acute pain studies include: (1) the evaluation of biomedical changes and pain reports during and following surgical procedures; (2) the effect of stress on the release of endogenous opioid peptides; (3) the mechanism of the placebo reaction; (4) the assessment of pain utilizing newly developed pain scales; and (5) the evaluation of anti-inflammatory agents and long-lasting local anesthetics in the control of post-surgical pain. Present chronic pain studies include: (1) the efficacy of tricyclic antidepressant drugs in the treatment of chronic pain, including painful diabetic neuropathies and post-herpetic neuralgia; (2) improved methods for the assessment and treatment of cancer pain in children and adults; (3) the evaluation and treatment of myofascial or craniomandibular pain and its differentiation from atypical facial pain; and (4) the mechanism of action of intracranial electrical stimulation for the treatment of intractable pain and its relationship to endogenous opioid pathways in the brain. Basic neurophysiological and neurochemical studies on mechanisms of pain transmission and modulation within the central nervous system (including studies of the role and function of endogenous opioids) are also needed.

Scientific opportunities also exist in studies of oro-facial motor function and dysfunction with a particular focus on efforts to increase our understanding of the central nervous system sites and mechanisms involved in control and modulation. Motor disorders include such conditions as TMJ problems, bruxism, and trismus and conditions arising as a result of systemic factors, drug side effects and infections.

Oro-facial pain problems continue to constitute a major component of acute and chronic pain problems in the United States. The economic costs of pain treatment and alleviation run into billions of dollars while its individual and social costs are huge and incalculable. TMJ disorders appear to afflict a significant portion of our population and, at present, health practitioners are often unable to deal effectively with the increasing numbers of people seeking treatment.

- Behavioral Approaches to the Prevention of Oral Diseases and Conditions

Research on the adoption, diffusion and implementation of preventive technologies and the development of innovative behavioral interventions for oral disease detection as well as for improved utilization of dental services are major areas of scientific opportunity. On-going and soon-to-be initiated studies are aimed at identifying factors influencing the adoption and implementation of school fluoride mouthrinse programs; establishing how dental practitioners learn

and adopt new disease-preventive techniques and evaluating the effectiveness of several behavioral interventions to improve long-term adherence to preventive regimens. Innovative behavioral interventions for oral disease detection will focus upon detection and education programs for high-risk population subgroups initially. Interventions for both preventive behaviors and the utilization of dental services will emphasize those utilization patterns consistent with health needs.

Research opportunities continue to exist in the prevention and treatment of dental fear and anxiety and on the nature of the dentist-patient interactions. Findings from recent studies show that desensitization procedures are successful in reducing anxiety in anxious dental patients and in lowering pain and shortening treatment time required for restorations. Specific behavioral techniques could be used to control gagging responses which had previously interfered with dental treatment and deterred patients from seeking care. Innovative cognitive coping and distraction strategies taught to child patients led to their cooperation and reduced anxiety during dental treatment sessions.

As scientific opportunities emerge, the need to form a critical mass at a research center uniting essential behavioral and social science disciplines--sociology, psychology, economics, epidemiology--becomes even greater. Such "centers of excellence" would facilitate the identification of behavioral and social risk factors associated with oral diseases or conditions; the development of cost-effective and efficient behavioral intervention strategies for oral disease prevention and health promotion; and the assessment of these interventions on oral health status and on their methodologies.

The crucial role of behavior on oral disease prevention and health promotion has been well documented. Understanding the many factors involved, and the development of successful interventions for the adoption, diffusion and implementation of preventive technologies should permit a more rapid application of preventive measures to the public. The development of interventions that would improve appropriate utilization of dental services and interventions that would allow for better detection of oral disease status would also contribute to the Nation's oral health.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

I. Major Program Changes, FY 1986

● Characterization of, and Biological Response to, Environmental Health Hazards

NIEHS plans new research initiatives that will be designated by forthcoming RFAs and program announcements. This will include:

- Support of research in the area of nutrition to elucidate the role of environmental agents in interaction with specific nutrients or other dietary components in producing adverse effects.
- Study of the structure, organization and regulation of genes and the mechanisms of their alteration by chemicals, and the development of systems for the early detection and potential consequences of cellular DNA damage by chemicals.
- Research to provide understanding of the role and mechanism of environmental agents on various aspects of the endocrine system including pancreas, neuroendocrine, thyroid and adrenal glands.

● Applied Toxicology Research and Testing

Particular emphasis will be placed on research aimed at improving the ability to explain toxic action at the sub-cellular level. This includes:

- Research to expand the capacity to detect mutations and further understanding of the mechanisms of mutagenesis.
- Research to improve understanding of the carcinogenic significance of proliferative liver lesions in rodents.

New research contracts are proposed in the following areas: chemical interactions; development and validation of additional in vitro and in vivo short-term tests; prechronic and chronic carcinogenic and other toxicological studies on chemicals of particular public health concern.

● Biometry and Risk Estimation

New work is proposed that will improve estimation of the biologically effective dose through research on molecular mechanisms that may be associated with chemically induced effects. Emphasis will include the expanded utilization of laboratory data on mechanisms of action for extrapolation to humans. A prime example of such work will be

laboratory research on dioxin through which it may be possible to quantify occupancy of receptors for dioxin as an indicator of biologically effective dose.

Efforts in biochemical and molecular epidemiology will focus on development and utilization of laboratory methods to: identify host factors (environmental and genetic) that influence susceptibility of defined populations to selected classes of toxicants using in vitro and in vivo systems; characterize early biochemical indicators predictive of responses to carcinogens and other toxicants; and, detect interactions of the active form of toxicants at the biochemical target site.

● Resource and Manpower Development

The NIEHS request level would provide for two additional Environmental Health Sciences (EHS) Centers. One proposed Center would be similar to those currently funded--it would be multidisciplinary in nature, directed toward major environmental health problems. The other proposed Center would provide a setting for combining basic and clinical research on people inadvertently exposed to toxic environmental agents. This Center would provide clinical care for patients while studies were being conducted to identify the agent(s) to which they were exposed, to identify biological markers and to conduct other research needed to assess possible health effects and methods of treatment.

The NIEHS request level provides support for 483 trainees. This is the same number of trainees funded in FY 1983, and allows NIEHS to meet more fully the growing need for well trained environmental toxicologists, epidemiologists, and veterinary pathologists.

● Intramural Research

Additional resources for intramural programs will be used to expand ongoing research and initiate new studies. This would include:

- The opportunity to capitalize on advances in nuclear magnetic resonance imaging by initiating a program to develop non-invasive techniques for detecting morphologic and metabolic changes in live rats and mice after chemical exposure.
- Expansion of research in molecular biology and biochemistry to enhance our understanding of how cells and other organisms react to toxic agents, thus improving the ability to estimate human health risks.
- Conduct of additional studies on immunologic response to toxic agents.
- Initiation of additional prechronic and chronic carcinogenesis and other toxicological studies.

- Expansion of studies on the effects of toxic agents on human growth and development.

II. Areas of Scientific Opportunity

- Mechanisms of Toxicity

The NIEHS Toxicology Research and Testing Program (TRTP) is placing particular emphasis on research aimed at improving the ability to explain toxic action at the sub-cellular level. This includes:

Continued efforts to expand the capacity to detect mutations and further understanding of the mechanisms of mutagenesis.

An ambitious program to improve understanding of the carcinogenic significance of proliferative liver lesions in rodents.

Scientists are now learning that there is a higher than anticipated genetic mobility in the DNA of many species which, depending upon the class of compounds, may be responsible for disturbances in growth. Research efforts will focus on trying to determine whether chemicals can induce insertion type mutations, which may play an important role in such disturbances.

In two year rodent toxicity and carcinogenicity studies conducted by the National Toxicology Program (NTP), liver tumors are the most frequently observed endpoint for determination of chemical carcinogenicity. Unfortunately, the mechanism (initiation, promotion, co-carcinogenesis) by which a chemical causes cancer cannot be determined in the two-year study. This work will develop a model for determining which chemicals initiate cancer and which chemicals promote cancer in previously initiated cells. It will also include identifying which early morphologic changes in rodent liver will ultimately progress to cancer.

A major issue in the study of genetic mechanisms of action is the need to know which of the various potential genetic mechanisms may be causally related to induction of neoplasia. Improved methods are needed to distinguish between various types of mutations and other genetic toxicity and their relation to carcinogenic and potentially heritable effects.

Currently, when a chemical produces hepatic nodules in rodents, it is impossible to determine whether that chemical initiates or promotes cancer. However, it is known that chemically initiated changes are permanent (but require promotion before cancer is expressed), whereas chemically promoted changes are not necessarily permanent. With a fuller understanding of the mechanisms of action, more effective intervention strategies can be developed.

● Human Health Risk Analysis and Estimation

There are important gaps in understanding events between exposure to an activated chemical and predicting toxic outcomes. NIEHS plans to focus on several aspects along this continuum.

New work is proposed in the Intramural Research Program, the Biometry and Risk Assessment Program, and the Toxicology Research and Testing Program that will improve estimation of the biologically effective dose through research on molecular mechanisms that may be associated with chemically induced tumors in animals.

Emphasis will be on the expanded utilization of laboratory data on mechanisms of action for extrapolation to humans. A prime example is research on dioxin through which it may be possible to quantify occupancy of receptors for dioxin as an indicator of biologically effective dose. Once we know how much functional receptor is occupied, we can use such information to integrate exposure data, relating it directly to mechanisms of action and subsequently estimating risk.

Efforts in biochemical and molecular epidemiology will focus on development and utilization of laboratory methods to: identify host factors (environmental and genetic) that influence susceptibility of defined populations to selected classes of toxicants by using in vitro and in vivo systems; characterize early biochemical indicators predictive of responses to carcinogens and other toxicants; detect interactions of the active form of toxicants at the biochemical target site.

The burgeoning knowledge of the molecular structure of gene sequences and rearrangements, and the causal association of macro-molecular interactions with certain tumors in animals and in cell culture, present the opportunity to shift some studies of dose/response to a more experimentally tractable system than the intact animal. There is now a need to utilize molecular systems to define the causal chain from exposure to initiation of biological damage.

In extrapolation from laboratory data to humans, increasing research emphasis has been placed on defining structure-activity relationships for the toxic actions of chemicals. Because of these efforts, the sequence of biochemical events ultimately leading to manifestations of toxicity is becoming more clear for some chemicals. By obtaining a detailed understanding of macro-molecular interactions in sensitive and non-sensitive species, predictions concerning human sensitivity might be possible. The use of state of the art mechanistic information, such as dioxin receptor interaction, could enable us to: remove some of the highly uncertain assumptions that are made in species extrapolation of risk including carcinogenesis; and more accurately predict non-oncogenic effects such as organ-specific toxicity.

NIEHS is in a unique position to utilize molecular and toxicokinetic techniques in the characterization of host factors that predispose or protect human populations from environmentally-mediated diseases. The Institute has the capacity to generate appropriate animal models to validate assay methods, and utilize direct collaborations of intramural molecular biologists, pharmacologists, epidemiologists and statisticians to investigate, in a comprehensive way, the underlying mechanisms responsible for epidemiological observations.

Even when environmental exposure can be defined, the variability of biological outcome among tissues and different species cannot always be explained. Understanding the metabolic events that lead to the biological activity of the carcinogenic chemical is only part of the equation; the genetic events (DNA-structure and gene regulation) that are associated with carcinogenesis must be factored into the dose/response relationship. This is probably the best approach that can be made on arriving at reliably predictive animal testing.

A great deal of uncertainty exists in the assumptions that are incorporated in risk analysis models because they are only as accurate as the quality and appropriateness of the toxicological data on which they are based. Moreover, there are significant limitations in the use of traditional epidemiologic approaches to study the environmental causes of disease. New approaches that integrate laboratory work evaluating pharmacokinetic data, factors that influence genetic predisposition, exposure data, and characterization of early biochemical markers should provide improved methods that reduce the uncertainty of predicting human risks to carcinogens and other toxicants.

NATIONAL EYE INSTITUTE

I. Major Program Changes, FY 1986

● Retinal and Choroidal Diseases

- Exploiting technological advances in the fields of molecular biology, cell physiology, and tissue culture in basic research on retinal cells and tissues.
- Assessing new drug and immunological approaches to the treatment and prevention of uveitis and other inflammatory disorders.
- Expanding biochemical and metabolic studies of Bruch's membrane (which separates the retina from the choroid), the adjacent retinal pigment epithelium, and the photoreceptors in the central retina, to provide new insights into aging-related maculopathy, other retinal degenerations, and retinal detachment.
- Intensifying the search for biochemical and genetic defects in retinitis pigmentosa and other hereditary retinal degenerative diseases, utilizing new molecular biology techniques.
- Characterizing neurotransmitters, the chemical substances that relay messages from one retinal nerve cell to another, with the aim of developing drug therapies for retinal neural disorders.
- Developing and applying better noninvasive tests of retinal physiology and of visual function in normal and pathological conditions.
- Performing studies of retinal capillary cells in tissue culture to elucidate the mechanisms of neovascularization, the abnormal growth of new retinal blood vessels, and the hemorrhaging that occurs in diabetic retinopathy, sickle cell retinopathy, and other vascular disorders.
- Conducting basic research on retinal detachment to determine what stimulates and controls the abnormal cellular proliferation and membrane formation in the vitreous humor that increases the damage in this condition.
- Assessing the damaging effects of environmental factors, nutritional deficiencies, and drugs on retinal function and developing screening systems for ocular toxicity.
- Pursuing new approaches to research on the basic biology, immunology, and genetics of sight- and life-threatening intraocular tumors.

- Corneal Diseases

- Determining the neuronal and viral factors contributing to the latent period of herpes infection.
- Continuing development of antiviral drugs and use of combinations of antivirals for treatment of acute and recurrent corneal infections.
- Continuing development of methods to stimulate repair of the diseased or injured corneal endothelium, especially in primates, and improving corneal transplant procedures using cultured endothelial cells as a possible replacement for donor tissue.
- Studying the biological effects of existing and proposed surgical procedures and optical devices for correcting refractive error.
- Evaluating immunological mechanisms of the ocular surface and their role in health and disease.
- Studying the frequently painful abnormalities of the ocular surface, their causes and persistence, and establishing their relationship to the cornea's neural supply.
- Investigating the changes that occur with disease and aging in the biochemistry of the corneal stroma.
- Improving understanding of the biochemistry and immunological components of the cornea's response to injury and wound healing, determining the importance of specific immunological factors in corneal transplantation, and developing and testing drugs which can modify or eliminate immune reactions to transplanted tissue.

- Cataract

- Determining through epidemiologic studies factors that increase the risk of developing cataract.
- Studying the molecular biology of the normal lens and cataract, with emphasis on gene analysis and the structure and metabolism of nucleic acids.
- Developing an objective system for classifying cataracts in the living eye as a standard for research on cataract prevention and treatment.
- Studying the biochemical and biophysical properties of lens crystallins, particularly with regard to transparency, and the structure and function of the cytoskeleton, those protein elements that help the lens maintain its shape.

- Studying the potentially cataract-inducing effects of low doses of ionizing and microwave radiation, and the effects of environmental ultraviolet radiation on the lens.
- Comparing the results of various methods of cataract surgery and employing controlled clinical trials to determine the safety and efficacy of various methods of optical correction following cataract surgery, including intraocular lenses, contact lenses, and surgical modification of corneal curvature.
- Conducting further studies of the characteristics of the enzyme aldose reductase and developing safer and more effective aldose reductase inhibitors to delay diabetic cataract formation.
- Glaucoma
 - Conducting clinical and laboratory studies to define genetic, racial, and environmental risk factors for the development of damage to the optic nerve in glaucoma and to determine the reasons for the varying susceptibilities of individual eyes to optic nerve damage.
 - Developing improved methods of detection and diagnosis and better drug and surgical treatments for glaucoma.
 - Devising new noninvasive clinical techniques for studying aqueous humor formation and flow, for continuous monitoring of intraocular pressure in man and in primates, and for studying experimental optic nerve damage in monkeys.
 - Studying the cell biology and molecular characteristics of the outflow tissues and their abnormalities in glaucoma, especially using tissue and organ culture techniques.
 - Exploiting experimental methods of studying the basic physiology and pharmacology of fluid movement in the eye and of controlling of aqueous humor inflow in primates and in man.
 - Investigating neovascular glaucoma and developing methods for its treatment.
 - Establishing eye donor programs so that appropriately obtained and preserved human tissues from well-characterized glaucoma patients will become available for correlations between clinical history and tissue damage and for cell biology studies.
- Strabismus, Amblyopia, and Visual Processing
 - Developing new or improved techniques for treating strabismus, including surgical, pharmacological, or other approaches; evaluating the most promising techniques in controlled trials; and determining how the timing of treatment influences its success.

- Developing and evaluating new treatments for amblyopia, including eye patching, contact lenses, or pharmacological approaches.
- Devising noninvasive methods for studying the development of visual processing in infants, particularly methods that could be used in the clinic for diagnosing and monitoring the effects of treatment.
- Studying the normal development and control of the eye movement system and the disorders that may affect it, especially using techniques that will aid in diagnosing eye muscle problems in newborns and young children.
- Determining the causes of and mechanisms responsible for the development of myopia in humans, expanding studies with animal models, and relating the results of animal studies to the human condition.
- Investigating the structure, function, and development of the visual system at the molecular level--including studies of cellular receptor sites, cell specificity, neurotransmitters and peptides, and immunological approaches--with the ultimate aim of designing drug treatments for visual neurosensory disorders and injuries.
- Studying the anatomy, physiology, and behavior of the systems that are important in vergence (moving the two eyes toward or away from each other to look at a nearby or faraway object) and accommodation (changing the shape of the lens to allow the eye to focus on an object) in normally developing infants as well as in those at risk for strabismus.
- Exploring the etiology of optic neuritis and optic nerve atrophy and those factors that may permit regeneration of the diseased or injured optic nerve.
- Intramural Research
 - Expanding studies of the characteristics of the enzyme aldose reductase (AR), which has been implicated in triggering various ocular complications of diabetes. Sorbinil, an aldose reductase inhibitor, will be tested as part of a multicenter clinical trial to determine whether this drug can slow or prevent the development of diabetic retinopathy in insulin-dependent diabetics who are at risk for the disorder.
 - oo Studying further the basic mechanisms underlying uveitis, in particular, those cases with a suspected autoimmune basis, and testing cyclosporine drugs in its treatment.

- Using recombinant DNA technology to study the pathological processes associated with specific eye diseases. Because intramural scientists have established a line of cultured human retinoblastoma cancer cells, one of the first problems that would be addressed is the identification of the substance that triggers the formation of abnormal cells in retinoblastoma.
- Utilizing fully NEI's inpatient and outpatient facilities in the Ambulatory Care Research Facility. This includes funds to purchase diagnostic and other equipment and supplies for patient care.
- Upgrading worn and obsolete equipment which is needed to take advantage of recent technological advances in the following areas: the search for biochemical and genetic defects in retinitis pigmentosa and other hereditary retinal degeneration diseases, using new molecular biology techniques; biochemical and metabolic studies of various retinal tissues to provide new insights into aging-related maculopathy, other retinal degenerations, and retinal detachment; the molecular biology of the normal lens and cataract; the development of visual processing in infants, particularly methods that could be used in the clinic for diagnosing and monitoring the effects of treatment.

II. Areas of Scientific Opportunity

● Molecular Genetics

The use of recombinant DNA techniques has begun to accelerate greatly the pace of vision research. These new methods may ultimately enable detailed understanding of the molecular basis for the development, the functional organization, and the expression and regulation of genetic information of the eye and the visual system. Many eye disorders--for example, certain types of cataracts, retinal degenerations, color vision defects, and retinoblastoma--are known to be hereditary. The identification and localization of the underlying genetic defects in these disorders present scientific opportunities of high priority.

- Study of Genes for Proteins of the Eye. Numerous gene families produce structurally and functionally important proteins of the eye. Recombinant DNA techniques are being used to study three such families, namely crystallins (lens proteins responsible for transparency), collagens (extracellular proteins controlling the shape and structure of the eye), and opsins (retinal proteins responsible for transducing light into nerve impulses). Numerous recombinant DNA clones containing cDNA and gene sequences for members of these families are now available and are being used to investigate evolutionary, developmental, and medical aspects of the visual system.

1. Crystallins. The construction of crystallin cDNA clones has made it possible to determine the genetic basis for the heterogeneity of the crystallins. Recent studies have shown that both gene duplication and alternative RNA splicing contribute to crystallin diversity. Sequence analysis has simplified our view of crystallin complexity by revealing homologies between crystallin classes (beta and gamma) which were believed to be unrelated. Crystallin expression is also being studied at the level of gene promoters. Special attention is being given to mice developing hereditary cataracts with specific defects in crystallin gene expression.
2. Collagens. Different collagens are present in different tissues of the eye. The basis for the differential expressions of the collagen genes is being studied with recombinant DNA probes. Emphasis is being given to the isolation and analysis of the Type IV collagen gene. Type IV collagen, as the key protein in all basement membranes, is responsible for the structure of epithelial tissues, and appears abnormal in diabetes.
3. Opsins. More is known about the role, structure, and physiology of rods and cones than about any other type of cell in the nervous system. In the past few years exciting advances have been made in clarifying the molecular events that control visual excitation and adaptation. Much of this research has focused on the roles of light-dependent interactions of rhodopsin with other rod outer segment biomolecules. The use of recombinant DNA techniques has begun to accelerate greatly the pace of this research. During the past year several groups have isolated DNA sequences which code for rhodopsin, and the primary structure of this gene has been determined. This achievement is an important first step which should quickly lead to an examination of opsin biosynthesis at the mRNA level, gene expression during development, and the isolation of genes encoding the protein moieties of the cone visual pigments.

Other investigators have begun to modify precisely the genetic code for opsin through site-specific mutagenesis. This will enable elegant analyses of the relationship between the molecular structure and the function of the visual pigments. Moreover, additional DNA cloning and sequencing will provide, for the first time, the primary structures of the cone opsins, and elucidate the genetic basis for color blindness.

Analysis of genes provides rapid knowledge of the primary structures of the major proteins of the eye. Without DNA sequencing, this essential information takes many years to obtain or, as in

the case of membrane proteins such as the opsins, is exceptionally difficult to obtain. Recombinant DNA technology allows extraordinarily sensitive methods to quantify, localize, and understand specific gene activity in the eye. Gene investigations reveal direct causes for hereditary visual defects. Finally, isolation of specific genes and knowledge of their developmental expressions pave the way for eventual therapy at the gene level.

- Molecular Genetic Investigations of Ornithine-delta-Aminotransferase Deficiency in Gyrate Atrophy. Gyrate atrophy is a rare autosomal recessive disease of the eye characterized by progressive chorioretinal degeneration and blindness. Hyperornithinemia and ornithine-delta-aminotransferase (OAT) deficiency have been demonstrated in patients with gyrate atrophy. Although the exact pathophysiological mechanism is not known, the elevated ornithine level is believed to be the cause of the chorioretinal degeneration. Thus, gyrate atrophy is a human degenerative disease of the retina and choroid in which a specific biochemical defect is known. Application of molecular genetic approaches will make it possible to examine the gene for the ornithine-delta-aminotransferase directly and eventually to determine the nature of the defect which results in the enzyme deficiency in the gyrate atrophy patients.

This pursuit is desirable for a number of reasons. First, research in the field of human retinal degenerations, which are major causes of blindness, has been very difficult due to lack of human tissue for study and the lack of knowledge of a basic underlying biochemical defect which may be contributing to the pathology. Gyrate atrophy, with its known OAT deficiency, is a unique exception. The OAT deficiency in gyrate atrophy appears to be a molecular genetic problem, not necessarily requiring eye tissue for study since other more readily available tissues from patients can be used. Second, clinical programs for gyrate atrophy patients have been established in the NEI's Clinical Branch and elsewhere. When the molecular probe for OAT is developed for examining patients' genes, these programs will become crucial. Finally, the elucidation of the molecular basis of this disease will be helpful in understanding other hereditary diseases of the retina and in applying molecular genetic approaches to understanding other eye diseases.

- Retinoblastoma. Retinoblastoma is the most common intraocular tumor in children. It is an unusual malignancy because there is a positive family history in some cases and in others it occurs sporadically. Recent evidence indicates that the gene for retinoblastoma is located in band q14 on chromosome 13. The use of a new method for detecting somatic genetic changes has provided strong evidence that retinoblastoma may result from the development of homozygosity for a mutant allele on chromosome 13.

Retinoblastoma is a malignant tumor that originates in the retinas of newborns and young children. Retinoblastoma may claim the vision or even the life of its victims. The incidence of this disease is between 1 in 15,000 and 1 in 28,000 live births. It is genetically transferred in virtually all bilateral cases and in about 10 to 15 percent of unilateral cases.

New studies of retinoblastoma are utilizing gene probes and other tools drawn from recombinant DNA technology to get closer to the root causes of this inherited blinding disease. These are basic, long-term studies that will lay the groundwork for clinical advances in the next decade and beyond.

National Eye Institute-supported grantees have been major contributors to a pioneering research effort that may provide the means to locate the genes responsible for these cancers and to identify at-risk individuals. Recombinant DNA technology has been used to generate new DNA markers that can be used to look for genetic differences between normal individuals and retinoblastoma patients. By using these markers and other molecular genetic techniques, investigators have localized the gene(s) controlling for retinoblastoma to a small region on chromosome 13. Investigators are now trying to determine how these genetic changes take place. The loss or inactivation of both alleles of the retinoblastoma gene is now thought to lead to the development of the tumor. Precise mapping of the aberrant gene(s) would lead to better genetic counseling of retinoblastoma families. A longer-term goal of such studies includes the identification of the aberrant gene product and an understanding of the origin of retinoblastoma at the molecular level.

- Neurobiology

NEI-supported vision researchers have been at the very forefront of neuroscience, frequently working in interdisciplinary teams representing such disciplines as biology, chemistry, psychology, biophysics, mathematics, engineering, ophthalmology, physiological optics, and neurology.

The preeminence of visual scientists in this exciting field is demonstrated by the 1981 Nobel Prize for Physiology or Medicine to two long-time NEI grantees, David Hubel and Torsten Wiesel, for their studies of the structure and function of the central visual pathways and the modification of these characteristics by the particular experience of the infant and, more recently, by the 1983 Lasker Award to NEI grantee Vernon Mountcastle for his studies on the organization of cortical cells into columns for processing sensory information.

- Synaptogenesis and Cell Death During Early Development of the Visual System. There are now exciting opportunities to study how the nervous system determines not only the pattern of connections among neurons but how many cells will differentiate and remain

active as a result of visual experience and competition between cells for target sites. There are far fewer viable neurons and synapses in the mature visual system than in infant animals, despite the greater visual capacity of the older animals. Recent studies using radioactively labelled dyes injected into the eye at specific points during fetal development of cats and monkeys have identified the progression of specificity in connections between retinal ganglion cells in each eye and cells in more central target structures. It will now be possible to determine the mechanisms that influence this increasing developmental specificity--a question of central importance to all of neurobiology. In addition, the question of how the number of neurons in the brain is regulated and whether this number is associated with the type of neuronal circuits that are developed can also be addressed.

Because many defects in visual processing have their origin very early in development, preventing and possibly curing them requires research into the way the visual neural structures grow and differentiate before birth and during infancy.

- Molecular Pharmacology of Retinal Neurons. Recent advances in biophysics now provide greatly enhanced opportunities to study retinal physiology and pharmacology at the molecular level. The newly developed technique of patch-clamping permits the measurement of the picoampere currents associated with single ion channels. In this technique, a tight seal between the tip of a glass micropipet and the cell membrane electrically isolates a patch (approximately $1 \mu\text{m}^2$) of membrane. With modifications of the technique, the glass micropipet can be removed from the cell with the patch left spanning the opening of the pipet tip. This allows single channel recording from isolated membrane patches in defined media. Alternatively, the region of the plasma membrane within the micropipet can be broken and, once this is done, the contents of the cell can be replaced with defined solutions.

In the application of patch-clamp technology to the study of brain cells, it appears very likely that studies of retinal neurons will be at the forefront. This is chiefly because considerable knowledge about retinal neurons in culture has been acquired in the last five to ten years. This is essential since, for various technical reasons, most patch-clamp studies must be done on enzyme-dissociated cells in culture. A further requirement for patch-clamping is the need to visually identify specific types of neurons in culture so that the same population of cells can be studied in each experiment. Fortunately, techniques for identifying a number of different types of retinal neurons have been developed. Few, if any, other regions of the brain have been as well studied in culture. In brief, the technology of retinal cell culture is ready for the technology of patch-clamping.

Specific opportunities for the application of patch-clamp technology to the study of retinal physiology and pharmacology include the identification and investigation of ion-channels linked to neurotransmitters and the analysis of the effects of transmitters, neuromodulators, hormones, nucleotides and drugs on the function of ion channels.

Malfunction of the retina is a leading cause of irreversible visual loss. Unfortunately, for the majority of patients with retinal problems, there is no pharmacological agent available to help with their visual difficulties. Thus, there is a pressing need to establish a scientific basis for the pharmacological manipulation of retinal function. Patch-clamp technology will help extend studies of retinal neuropharmacology to the molecular level.

- Studies on Isolated Retinal Neurons. The combination of technological advances in electrophysiology, neuropharmacology, and cell biology has led to the recent development of methods for exploring the function of single retinal neurons. By using state-of-the-art techniques, the opportunity exists to control experimentally an isolated neuron's exposure to a variety of input signals (neurotransmitters, neuromodulators, or selected drugs) while simultaneously monitoring the effects of these inputs on specific ion-channels and on the output of neurotransmitter. This powerful approach for examining many aspects of the input-output process of a single neuron should produce important information concerning the receptors for neurotransmitters, the membrane properties of neurons, the ions involved in the generation of potentials and possible mechanisms for the long-term modulation of neuronal activity.

Advances in cell culture methodology have also helped to learn how the development of retinal synapses may be regulated. The ability to control culture conditions has permitted the identification of defined steps in the functional maturation of synapses made by a specific class of retinal neurons. Recent experiments have revealed that both systemic and local signals may interact to regulate the turning of events in the development of a functional synapse. Opportunities now exist to analyze, at the biophysical level, the effects of developmental signals.

The retina is the best studied region of the brain for identifying specific types of living neurons in culture and for analyzing the function of isolated nerve cells. The general experimental strategies developed to study retinal neurons in culture should be applicable to studies of neurons from other regions of the brain.

The ability to study isolated retinal neurons facilitates the identification and investigation of molecules that can regulate the function and development of retinal neurons. Knowledge of

regulatory molecules is likely to be important in establishing a scientific basis for a pharmacological approach to the prevention and treatment of retinal dysfunction.

- Immunology

Ocular immunology has become well established as an exceptionally important area of research. Ocular immune models provide the investigator with a powerful tool for studying cellular and humoral mechanisms of disease. Because these systems are particularly "clean," they provide the researcher with answers that might not be obtainable in other systems. Because many disease processes in the eye are similar to those in the rest of the body, several observations in ocular models are relevant to immune functioning in general. The important question of the eye as a so-called immune "privileged site" has been fundamentally questioned, and these new models have demonstrated active suppression of the immune response when a foreign antigen is placed into the eye. These findings have a major impact on our understanding of graft rejection or its tolerance. Techniques such as cell culturing, T-cell cloning, and hybridoma technology have provided the researcher with a wealth of new approaches for exploring many questions in ocular immunology. Monoclonal antibodies have been utilized in the study of immunoreactive cells in the eye. The cloning of cells that produce interferon has also provided researchers with a valuable method in which an immune product of the lymphokine cascade can be utilized to treat herpes simplex keratitis, the most common serious infectious corneal disease in the United States. The relevance of ocular immunology to other areas of eye research is great; the techniques developed in the field can be utilized by many others in the study of ocular disease and normal ocular mechanisms.

The use of S-antigen-induced experimental autoimmune uveitis has provided the researcher with a reproducible animal model for ocular disease. The finding that T-cell mediation is important in this disease led to the use of cyclosporine in this animal model. The prevention and abrogation of this severe immune-mediated model by cyclosporine has led in turn to the hypothesis that this drug might be useful for selected cases of human endogenous uveitis. Since these patients demonstrated evidence of retinal autoimmunity, it was logical to assume that immune mechanisms similar to those in the animal model may be at work. Preliminary results indicate that cyclosporine can be used successfully in patients with severe bilateral uveitis. Patients who have failed on either systemic corticosteroid or cytotoxic therapy have responded positively to this medication. It has also been found useful in the treatment of children with uveitis where the only alternative might have been cytotoxic agents. Because of these findings and those demonstrating cyclosporine's efficacy in preventing solid organ rejection, it is reasonable to hypothesize that corneal graft rejection may be prevented with the use of this medication. A randomized masked study is underway at the NEI Clinical Branch to test this hypothesis in patients who have had graft failures. Also, the demonstration that

in some patients with retinitis pigmentosa this immune system may play a role in modulating their disease has prompted the use of cyclosporine in an attempt to either decrease or reverse the disease process for which no treatment exists at present.

Ocular immunology is just beginning to flourish. The advances made in the recent years demonstrate the importance of this area. Techniques that are applicable within ophthalmology and outside will continue to be developed and will help define areas of normal and abnormal immune response.

Areas of Scientific Opportunity

● Structure-Function Relationships of Proteins

One of the goals of biochemistry has been to interpret molecular structure in terms of function. This has taken two largely independent tracks. One is the development and application of techniques, most of which came from physics, to determine macromolecular structure. The other track is classical biochemistry, analyzing the chemical basis of biological function.

Some recent examples of the convergence of these two approaches can be seen in the area of protein-nucleic acid interactions. The structures of the proteins that regulate gene expression have been obtained by x-ray diffraction techniques. Knowledge of these structures has suggested some possible mechanisms of action. One study has been reported of the interaction of a regulatory enzyme with a twelve nucleotide-long DNA segment, and other similar studies can be expected.

A major element linking structure and function is the development of recombinant DNA technology. The ability to utilize site-specific mutagenesis makes it possible to selectively evaluate the effects of structure on function. This is now being studied in a number of laboratories where the modified enzymes (proteases, beta-lactamase) will be analyzed through a variety of physical techniques.

Finally, site-specific mutagenesis promises an opening into some previously intractable problems in the analysis of protein folding. The ability to selectively alter structure provides the opportunity to test models of protein folding in a realistic way. Coupled with new methods for picosecond measurement, pathways for folding may now be discernable.

● Eukaryotic Genes

Some recent trends in the direction of fundamental genetics research, outlined below, provide both an indication of the direction of future investigations, and, concurrently, opportunities for supporting new and important sorts of scientific endeavors. Molecular genetics, particularly, is now beginning to have some impact on our understanding of disease, and this discipline can be expected to have an increasing impact on biomedical research.

- There has developed a growing capability to study organisms with highly complex genomes. In the past, the premier organisms for the study of fundamental problems in genetics at the molecular level have been *Escherichia coli* (genome size 9000 kilobase

pairs) and its viruses (genome size 5-200 kb). Methodology developed in the past decade, including many aspects of recombinant DNA technology and DNA sequencing, permit similar levels of sophisticated work on far more complex organisms, such as yeast (12,500 kb), drosophila (165,000 kb) and human cells (2.9 million kb).

- More complex biological problems are being studied. Past interests in molecular genetics have centered on the relationship of genes, gene products and their controlling elements. Thus, classical work on topics such as lactose utilization and tryptophan synthesis in *E. coli*, and the molecular aspects of bacteriophage infection form a brilliant fabric of Nobel-prize quality research from ca. 1950 to 1980.

More recently, there has been some trend towards attempts to attack problems of neurobiology and behavior at the level of molecular genetics, using animals such as nematodes, sea slugs and, particularly, drosophila.

- New concepts of cellular development and morphogenesis are arising out of research in genetic switches (for example, mating types in yeast) and transposition of gene fragments in immunology. The hope of the early embryologists that their field of study might be understood in chemical terms now has some chance of fruition, albeit 50-100 years later. Findings in this-area may throw new light on abnormalities in development, and on the mechanism of teratogens.

- Cytoplasmic Structure-Function Relationships

Advances in high resolution electron microscopy, coupled with superb state-of-the-art biochemistry, have changed our picture of the cell. Cytoplasm has been revealed to consist of densely packed masses of electron-dense material. Rods, filaments, and tubules abound, with diameters ranging from one-millionth of an inch down to the limits of staining and resolution, perhaps one ten-millionth of an inch. Often these structures form a network, or appear in bundles, perhaps connecting different classes of filaments or fibers. The structures are not necessarily fixed, but seem to be capable of synthesis and dissolution depending on the state of the cell.

Most exciting have been the isolation and purification of the cellular proteins, and the reconstitution of filament, tubule and other structures in vitro. The microtubules, for example, have been particularly well studied, and the conditions for their assembly and disassembly from tubulin and associated proteins has received a great deal of attention. It is possible in vitro to mimic the assembly of the spindle and mitotic apparatus. The reconstitution has often been surprisingly successful and revealing. For example, a protein named clathrin has been isolated from coated secretory vesicles. Clathrin can self-assemble into basket structures of approximately the same dimensions as the coats around secretory vesicles.

The advances in monoclonal antibody technology, and specific cytochemical stains, have allowed investigation of the specific distributions of these identified proteins. For example, one protein, vimentin, which assembles into intermediate filaments can be seen to form a network around the cell nucleus, perhaps even extending through the nuclear pores. This is especially intriguing in view of vimentin's ability to bind nucleic acids. Chemical identification, particularly using specific antibodies, reveals similarities or identity of cytoskeletal proteins across tissue types. Actin, a major muscle protein, has been isolated from a wide variety of cells, and characteristic actin filaments are found wherever cell motion occurs. Other major muscle proteins, such as myosin, tropomyosin and tropinin-like proteins, also can be found in these cells. Every month a new cytoskeletal protein is being found and named, and its role explored. Names like desmin, filaggrin, profillin, gelsolin and ankyrin appear. Some proteins seem to form distinctive structures, some may regulate other structures, and a few show evidence of bridging two classes of structure.

Much effort has been directed to control of subunit assembly and association and regulation of cell movement. Although such control involves many processes, of special interest is the role of calcium. It is becoming ever more evident that calcium is a major regulator of intracellular activities. Intracellular calcium activity is maintained at a very low level. Increased activity can effect a wide variety of changes in numerous classes of cells--secretion, photo-reception, potassium transport, mitosis, contraction, microtubular polymerization, among others. Major questions currently being addressed are: How is intracellular calcium activity maintained at its extremely low level? How is the transient increase brought about, i.e., how is membrane permeability increased or calcium stores released? How do slight changes in calcium level control such a wide variety of events? Lastly, what cellular events are calcium-sensitive? Among the approaches to finding answers to these questions is the use of genetic variants of macrophage cell lines with altered calcium sensitivity, which is turning out to be a powerful tool in studies of the role of intracellular calcium.

- Role of Metals in Biological Processes

Chemists and biologists are joining forces and technology to decipher the contribution of metal complexes to biological processes. Enzymologists have studied the rates and molecular mechanisms of enzyme-catalyzed reactions for many years, and have been aware that metal atoms, especially iron, were somehow involved in the active sites of these enzymes. However, recent advances in both analytical technology and bioinorganic chemistry have combined to thrust the study of the submolecular mechanism whereby metals participate in biological reactions into the forefront of basic biology and chemistry.

Iron is one of the most important metals in terms of biological function, especially enzymatic oxidation-reduction reactions. Iron, particularly bound to a porphyrin prosthetic group, forms the active

site of such diverse molecules as hemoglobin, peroxidases, cytochromes, and catalases. Utilizing physical, chemical and genetic methods, scientists now have the potential for elucidating the events at the electronic level which modulate and control the rates of those reactions most basic to the cellular life process, the electron transport chain and oxygen transport and utilization within the cell.

While iron-porphyrin complexes have received, and are receiving, the greatest amount of attention from investigators, other important and fascinating systems are also beginning to garner increased attention. Some of these include non-heme iron-containing enzymes such as a hepatic microsomal FAD-containing monooxygenase, bacterial dioxygenases, and non-heme lacunar iron complexes which mimic heme-protein functions. Molybdenum is another metal which is found, often combined with iron and sulfur, at the active site of many diverse enzyme molecules such as sulfite oxidase, nitrate reductase, xanthine oxidase, and aldehyde oxidase. Other intriguing biological molecules combine copper, zinc, manganese, or cobalt with complex organic ligands.

The area of bioinorganic chemistry is beginning to explode with excitement and potential in all areas. The Nobel Prize in Chemistry for 1983 was awarded to an NIGMS grantee, Henry Taube of Stanford University, whose work has formed the theoretical basis for beginning to understand the way in which the attachment of metal ions to biological molecules affects the chemical reactivity and biological properties of the entire complex. Advances in methodology such as electron paramagnetic resonance, extended x-ray absorption fine structure spectroscopy (EXAFS), resonance Raman spectroscopy, nuclear magnetic resonance, and fast reaction kinetics, as well as synthetic techniques and biological approaches such as recombinant DNA and gene cloning have brought the field to the point where significant advances can be anticipated in the immediate future.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

I. Major Program Changes, FY 1986

At Level 5 (Enhancement Level II), the NHLBI will fund forty-five percent of its approved competing research project grants which represents an increase of 328 over Level 4 (Enhancement Level I).

At this level, a number of new research initiatives can be pursued.

Investigations are planned on basic mechanisms that underlie atherogenesis and related phenomena with particular emphasis on the role of vascular endothelium. The endothelium of the large arteries, such as the aorta, coronary, cerebral, and others involved in atherogenesis and (or) in coronary heart disease, covers a relatively small area and, unlike lung endothelium, cannot act as a metabolic organ influencing systemic metabolism. Its behavior as a selectively permeable membrane does not involve major fluxes, the effect being limited to exchanges of local tissue interest. These local phenomena, however, are of critical importance to pathological events that express themselves as atherogenesis, arterial thrombosis, and arterial vasomotion (spasm or relaxation). The vascular endothelium offers numerous opportunities for study and it is hoped that new information derived from this initiative will contribute to the prevention of atherogenesis and its sequelae of heart attack and other ischemic diseases.

Smooth muscle and endothelial functions in normal and injured lungs will also be a focus of investigation. Among the opportunities for the future are studies on: the full range of metabolic activities of pulmonary and systemic endothelium; physiological and clinical implications of alterations in the capacity of the pulmonary endothelium to process circulating substances; factors that determine the permeability of pulmonary endothelium in the normal and injured lung; and the role of endothelium in the inflammatory response. Additionally, the Institute would initiate research on airway smooth muscle tissue. There is no entirely satisfactory model of asthma or asthmatic muscle largely because the etiology and pathogenesis of asthma is not fully understood. Airway smooth muscle contraction and the extreme sensitivity of the airway smooth muscle responses to various stimuli are accepted as key factors in other diseases such as bronchitis and cystic fibrosis. Numerous opportunities for research with emphasis on neurophysiology and pharmacology have been identified. Investigations of the neural network are planned as are studies on potential causes of abnormalities in asthmatic muscle such as alterations in membrane channels and receptor transduction processes. Research will be encouraged to clarify the role of inflammation and inflammatory mediators in disease of airway smooth muscle.

The Institute would also issue an RFA to support a Pilot Study on Non-invasive Techniques in Sickle Cell Disease. Substantial improvement in medical imaging technologies has occurred in the last few years and non-invasive imaging techniques provide opportunities to study certain manifestations of sickle cell disease in vivo. Positron emission tomography, nuclear magnetic resonance, and thermography offer new prospects for studying blood flow and metabolism in tissues and organs. Results of such studies could lead to the development of methods for following the status and progress of sickle cell disease including changes characteristic of the recurrent sickle "crisis." This proposed pilot study has as its objective the determination of the usefulness of these new noninvasive techniques for investigating the pathophysiology of sickle cell disease and for monitoring blood flow in various tissues and organs in the clinical evaluation of the sickle cell syndrome.

An RFA on Mechanisms of Platelet Refractoriness is planned. It is well established that platelet transfusions are effective in controlling bleeding in thrombocytopenic patients. The ability to provide platelets as a separate transfusion product and to maintain an adequate inventory has led to increased use of this product. Ineffective or unnecessary transfusions, insofar as they contribute to alloimmunization, may significantly compromise the care of thrombocytopenic patients. It is essential, therefore, to ensure that platelets are used only when necessary to provide hemostasis, that these platelets are histocompatible with the recipient, and that other conditions that would destroy transfused platelets are recognized. The subject of this initiative is twofold. First, it is important to determine factors that produce refractoriness in transfused patients. Studies are needed to identify the specific mechanisms involved, the frequency with which each event occurs, and the tests that can be used to determine appropriate treatment. The second objective is to identify methods to improve platelet support for refractory patients. Studies will address the provision of "compatible" platelets for alloimmunized thrombocytopenic patients and the prevention of nonalloimmune platelet refractoriness.

At this level, the first substantial growth in research training since FY 1980 will be realized with an increase of full-time training positions (FTTPs) by 50 for a total of 1,670 FTTPs.

The Institute will also begin summer programs in pulmonary and cardiovascular research for minority students. The purpose of these programs is to introduce qualified undergraduates to careers in research and to encourage their career development.

Programs in research career development will be expanded to include a pulmonary basic scientist award, a preventive pulmonary basic scientist award, a preventive pulmonary academic award, and a special emphasis career award in biomaterials.

The Minority Biomedical Research Program will receive an increment to encourage research among investigators at minority institutions.

At this level, it will be possible for the Institute to allow competition for successful NHLBI Specialized Centers of Research (SCOR) program grantees to become National Research and Demonstration Centers by adding a demonstration and education component to their existing basic and clinical research programs.

II. Areas of Scientific Opportunity

● High Frequency Ventilation

Since World War II, mechanical ventilators that mimic normal breathing in awake humans have become invaluable tools in the nation's operating rooms and intensive care units. Nonetheless, there are certain diseases and certain operations for which these ventilators are ill adapted or for which they seem to produce serious side effects.

Recently, a new type of ventilatory support has been devised that shows promise for some of the situations in which standard mechanical ventilation is a problem. Known as High Frequency Ventilation (HFV), this new technique relies on the use of very small tidal volumes (as little as 1/3 to 1/30 of the volume used in conventional ventilators) delivered at frequencies as high as 60 breaths/second.

In air breathing animals such as man, the gas exchanging surfaces (the alveoli) are separated from the environment (air) by a set of conducting pipes--the nose, mouth, throat, trachea, and bronchi. Roughly the first third of each resting breath is "wasted" just in clearing out this so-called "dead space" before fresh air can be delivered to the alveoli to effect the exchange of oxygen and carbon dioxide.

Early mechanical ventilators were designed to imitate natural breathing as closely as possible--about 12-15 breaths/minute with volumes of about 500 ml for a typical adult; up to 80 breaths/minute and about 20 ml for newborns. Again, about one-third of each breath is needed to clear the dead space.

Since the volumes being moved during HFV are often less than the theoretical volume required to clear the dead space, the means by which oxygen and carbon dioxide are exchanged during HFV thus far have defied rigorous explanation. During normal breathing, all parts of the lung are synchronously and uniformly inflated at the end of inspiration and all parts are relatively deflated at the end of expiration. The major factor that determines the magnitude of local lung expansion is the compliance (expansibility) of each of the lung segments. During HFV, the different resistances that the many different sized air passages offer to air flow and the inertia of the moving air as it oscillates at high frequency become important factors in determining regional lung expansion and hence gas exchange. Such asynchronous emptying and filling of excised dog lungs has been documented with stroboscopic motion picture photography. The present

belief is that gas movement into and out of all the alveoli during HFV is nearly twice the volume delivered at the trachea. Reaching an understanding of how HFV works is a challenge to bioengineers and respiratory physiologists, whose efforts in this area are likely to advance considerably the field of respiratory physiology in the years to come.

What Safety Features Should Be Considered?

Theoretical and experimental research on the dynamics of gas flow during HFV has found that even though gas exchange can be accomplished with low pressure in the upper airways, the pressure in the alveoli may at times "build up" and be manyfold higher than expected. It was shown that pressures in the alveoli can be as much as four times the pressure measured at the trachea. This pressure peaked at what could be considered the resonant frequency of the lung. Further investigation demonstrated that this resonant frequency varies with the degree of lung inflation and with changes in airway resistance. Thus, if a single frequency were to be used in all patients, the pressure in the alveoli and the effectiveness of gas exchange is likely to vary widely and perhaps dangerously.

Several other factors related to the safety of operation of high frequency ventilators also need to be considered, particularly the potential for kinking and blocking of the tubes involved. Many existing HFV devices use high flow rates, and the danger of hyperinflating the lungs is a serious one. Alarms and automatic pressure relief valves should be incorporated. Another problem is that such ventilators may work so well that too much oxygen enters the bloodstream with the resulting risks of toxicity. Monitoring of oxygen and carbon dioxide levels in exhaled air is normally sufficient with standard ventilators to prevent such an occurrence. With HFV, the composition of exhaled air cannot be predicted to reflect arterial blood levels of oxygen and carbon dioxide, and HFV requires the development of other monitoring devices. The reliability of high frequency ventilators must also be given careful attention, since the demands of operating at such high frequencies would be expected to lead to more frequent equipment breakdowns. In addition, the interaction of machine and patient must be considered.

When Should HFV Be Used?

Because HFV can produce very favorable gas exchange with lower airway pressure and smaller volumes than are used with conventional ventilators, it also offers promise as a more effective ventilatory support to premature infants with underdeveloped lungs. As many as 20 percent of premature infants of weight below 2,000 grams who are on conventional ventilators develop a dependency on oxygen that can last anywhere from 1 month to 3 years. Based on preliminary clinical studies, there are reasons to believe that HFV could significantly reduce the incidence of this oxygen dependency, but because the

superiority of HFV has not been established and because of uncertainties regarding its possible side effects, its routine use has been discouraged by experts who recently evaluated the entire HFV field. It has been strongly recommended that a carefully planned, controlled clinical trial be conducted involving multiple centers.

- Basic Defect(s) in Cystic Fibrosis

Opportunities now exist for attempting to identify the basic defect(s) in cystic fibrosis (CF) through pathophysiologic studies employing novel cell, organ, and tissue cultures, and transplantation techniques.

Cystic fibrosis is the most frequent lethal childhood genetic disease in white Americans. Currently, there are an estimated 30,000 CF patients in the United States. Pulmonary disease such as cough, wheezing, pulmonary infections, and respiratory obstruction is one of the major diagnostic criteria for CF, and it eventually occurs in all patients although it may be absent at the time of initial diagnosis. Advances in therapeutic and management modalities have steadily increased the life span of CF patients from about 2 years in 1940 to more than 20 years in the 1980s. Thus, over 20 percent of CF patients are now adults. Almost 5 percent of the white American population is believed to carry the abnormal gene. The only way to identify such carriers is through family histories of the incidence of the disease. Thus, unless the carriers of the CF gene can be identified early and counseled, the incidence of CF is unlikely to decrease.

The basic defect or defects giving rise to cystic fibrosis are unknown. While impressive advances can be cited in the clinical, diagnostic, and therapeutic areas, investigations of the basic defect are still marked by extremely slow progress and by uncertain and often conflicting results and claims.

Current Approaches and Opportunities for Innovation

The necessary limitations of research on human patients make it imperative that new approaches be developed for replicating the abnormalities associated with cystic fibrosis in cells, tissues, or whole animals. Basic research to determine CF-associated aberrations has thus far been confined to the cellular level. These studies have led to interesting information but as yet to no major breakthrough.

In studies of parotid acinar cells, the calcium content of CF cells was twice that of the controls. These observations suggest that an abnormality in the handling of regulatory calcium by exocrine tissue may be the primary defect in CF. However, there is no generalized abnormality of calcium metabolism in CF although it could occur specifically only in secretory cells. Biochemical and other studies with various individual cells from CF patients are continuing, but the biochemical marker or the cell type reflecting the defective gene

has thus far been elusive. Recent developments in cell cloning and in genetic and monoclonal antibody technologies open up new avenues for study.

Many studies have been conducted on biopsied tissues from various CF organs. A hindrance to progress in this approach is the lack of culture methods for maintaining the tissues and organs in a state close enough to that in vivo to permit biochemical or physiologic measurements. Recent studies with isolated nasal epithelia from CF patients and comparison with those of patients and siblings of patients (heterozygotes), normal individuals, and parents with other (non-CF) pulmonary diseases have revealed significant differences and indicate that this approach could prove useful. A series of studies conducted on the bioelectric properties of, and unidirectional fluxes across, nasal epithelia excised from CF patients pointed to a possible defect in chloride permeability in CF epithelia and suggested that CF epithelia do not absorb sodium ions but have decreased chloride ion permeability. The above conclusions were confirmed with CF sweat-gland both biopsied and in situ. Studies of drugs and agents that influence electrolyte transport across the epithelium including their efficacy, toxicity, and modes of delivery will be an exciting area of research.

Thus far, no animal model exists that will mimic all the CF abnormalities simultaneously, although several have been reported that either spontaneously or after some pharmacologic treatment exhibited one or more of the pathologic features. The best-studied "animal model" of CF is the chronically reserpinized rat. The model was highly susceptible to pneumonia but never developed the specific pulmonary infections as do children with CF. However, following transtracheal introduction of agar beads containing *Pseudomonas aeruginosa*, animals developed chronic infection and mimicked the histopathologic patterns associated with pulmonary infections with this agent in humans but none of the other abnormalities associated with CF.

A way may have been found to overcome conceptual and practical problems associated with existing "animal models" of CF. In recent preliminary studies employing tissue transplantation techniques, which were found to be quite successful in cancer research, it has been demonstrated that CF tissues such as respiratory mucosa can be transplanted successfully and maintained in immunologically incompetent animals ("nude" mice) without apparently altering their functional properties. Development of this approach would require: access to diseased and normal human tissues, with registries of patients to serve as donors and careful records of their clinical status; reliable methodology for the collection, transport, and storage of tissues; and processing of results. Future challenges and opportunities for CF research rest in novel biological, genetic, and immunologic techniques, cell and organ culture, tissue transplantation, and tissue banking technology.

- Molecular Mechanisms of Myocardial Hypertrophy

Recent advances that enable the examination of genetic control mechanisms make it possible for molecular biologists and cardiologists to jointly study the genesis of cardiac hypertrophy and investigate fundamental mechanisms of its development.

Approximately fifty percent of deaths in the United States are the result of cardiovascular disorders. Both direct health care costs and total cost to the U.S. economy are staggering, with current annual estimates placed at \$37.9 billion and \$96.9 billion, respectively.

Cardiac hypertrophy, or enlargement of the heart, occurs in response to the imposition of an increased workload. This compensatory process is the result of increased size of individual cardiac cells rather than by cellular proliferation. Hypertrophy ranges in its extent and severity from that produced by the relatively mild stimulus of heavy physical labor or exercise to that produced by very substantial increases in workload as a result of such conditions as congenital heart disease, uncontrolled hypertension, valvular stenosis, or incompetence. When cardiac performance in the face of added workload does not match circulatory demands, heart failure develops. In this syndrome, cardiac output is not sufficient to match body needs. Thus cardiac hypertrophy is often a prelude to congestive heart failure, a serious, largely incurable disorder that results in substantial morbidity and early mortality.

One aspect of hypertrophy involves not only the muscle cells but also the blood vessels that supply the enlarging muscle mass and the connective tissue skeleton of the heart. The former finally fail to keep pace with the muscle mass, and the latter finally constrict the mass and interfere with compliance. The tissue factors that modulate this compensation and ultimately pathological organogenesis are not understood. It is of some interest that in animal experiments, anti-hypertensive drugs appear to influence the development of cardiac hypertrophy differently and independently of the blood pressure itself. This observation may provide a clue to the molecular mechanisms of hypertrophy and to therapy when the heart is a target organ in hypertension.

Better diagnostic procedures, improved therapeutic techniques, and strategies for more effective prevention of congestive heart failure require clear understanding of the basic process of myocardial hypertrophy. Recent observations indicate that cardiac hypertrophy involves changes in gene regulation and gene expression. Insight into the mechanisms of cardiac hypertrophy will require investigation of basic cellular events. As initial studies demonstrate, research directed toward the elucidation of fundamental events involving gene organization, expression, replication, transcription, mRNA processing, and protein synthesis offers great opportunities for understanding the basic mechanisms of myocardial hypertrophy. These investigations

employ recent advances in recombinant DNA technology, DNA sequencing techniques, and monoclonal antibody production. At the present time, few cardiovascular investigators employ such techniques, and molecular biologists have yet to focus their attention on cardiovascular problems.

The following research areas are key examples of the many possibilities that warrant investigation:

- (1) The organization and control of expression of gene families (such as isomyosins and isoactins);
- (2) The physiological and pathological consequences of cardiac isozyme transitions;
- (3) The control of cardiac protein synthesis and degradation;
- (4) The isolation and characterization of the stimuli that initiate hypertrophy, and their receptors;
- (5) The sequence of biochemical events that leads to gene activation once an initiating factor binds to its receptor;
- (6) The determination of whether different initiating factors operate through entirely separate mechanisms or if their mode of action intersects at a common control point; and
- (7) The identification of factors that determine whether and when the hypertrophied heart fails.

● Thrombosis and Hemostasis: Platelet Disorders

Many advances in the understanding of normal hemostasis have occurred during the past decade. Two opportunities now exist to build on this information and transfer it to the clinical setting. The first is to elucidate the pathogenesis of clinical disorders, such as thrombocytopenia, in which platelet abnormalities may be involved, and the second is to support fundamental and basic research in blood-vessel-wall biology.

Severe thrombocytopenia develops in a large number of clinical circumstances. One such illness is the sudden, life-threatening thrombotic thrombocytopenic purpura (TTP). Its pathogenesis, with implications for understanding the processes that normally prevent thrombi from forming in the microcirculation, remains undefined. The allied condition of adult idiopathic thrombocytopenic purpura (ITP) is somewhat better understood, and recent developments in long-term therapeutic approaches can reduce the risks of bleeding. Further advance would include the availability of reproducible, simplified methods for measuring platelet-bound IgG that should permit a definitive evaluation of this test in diagnosis and clinical management.

Little is known today about the cause of abnormal platelet function in uremia. Production of prostacyclin by vessel segments was recently reported to be increased in uremic patients and thus may have some bearing on the problem. Cryoprecipitate as well as some non-plasma-derived products are now being tested and used for control of uremic bleeding, but the mechanisms by which these products work are unknown.

Knowledge of the physiology, biochemistry and immunology of the platelet has been increasing steadily. The level of understanding of the role of the platelet in conjunction with other hemostatic factors has advanced to the point where the application of this knowledge to the clinical disorders described above would be fruitful.

Platelet adhesion to subendothelial tissue is now known to involve binding sites on collagen and other subendothelial materials, on the large multimers of von Willebrand protein, and on glycoprotein I of the platelet surface membrane. Little yet is known at the molecular level, however, about the interactions of these binding sites. The mechanisms by which individual platelets adhere to each other during platelet aggregation are better understood at the molecular level. How binding of fibrinogen and binding of thrombospondin derived from platelet alpha granules, acting together or separately, cause platelets to adhere to each other still is not clear. It is now well established that stimulated platelets secrete many different materials from their alpha-granules and dense bodies during aggregation. Some of these materials are unique to the platelet, whereas others are present in far greater amounts in the plasma. It is not clear as yet whether selective binding of these platelet-secreted materials occurs during hemostasis--that is, whether these platelet coagulant proteins have a unique function unlike that of their plasma counterparts.

Although new culture techniques make it possible to study in vitro the mechanisms controlling the differentiation and maturation of megakaryocytes, such studies are still few in number. The potential of this technique for studies of the physiology of platelet production in normal and pathologic states still has not been fully exploited.

Specific research needs and opportunities include:

- (1) Elucidation of the pathogenic mechanism for thrombotic thrombocytopenic purpura and related syndromes and evaluation and standardization of plasma exchange and infusion therapy for these disorders;
- (2) Characterization of platelet antigens and the antigenic specificity of the antibodies arising in patients with idiopathic thrombocytopenic purpura;
- (3) Determination of the pathogenesis of bleeding in uremia; evaluation and standardization of the management of uremic bleeding, and further evaluation of therapeutic outcomes;

- (4) Improvement of platelet transfusion therapy through clarification of indications for use; improvement of methods of preparation and storage of platelet concentrates; development of methods for pre-transfusion cross-match; and development of methods to prevent and detect immunization to platelet antigens and contaminating lymphocytes;
- (5) Investigation at the molecular level of the structural properties and biochemical reactions of platelets important for platelet adhesion and aggregation;
- (6) Determination of the appropriate uses for tests of activation of platelets by measurement of platelet factor 4 and beta thromboglobulin, and activation of blood coagulation by measurement of fragment E in the prevention, diagnosis, and treatment of thrombotic disorders; and
- (7) Expansion of studies of the differentiation and maturation of megakaryocytes to further understanding of the physiology of platelet production in normal and pathologic states.

● Molecular Basis of Myocardial Contractility

A large number of studies now suggest that the same basic mechanism underlies the contractility of a wide variety of different systems. Processes as divergent as cell division, cytoplasmic streaming, and clot retraction on the cellular level may be driven by the same basic mechanism that drives the contraction of skeletal muscle, vascular smooth muscle, and cardiac muscle on the organ level. Motion occurs in these systems when two sets of interdigitating filaments--the thin actin filaments and the thick myosin filaments--slide past each other. Because the contractile system is so widespread, it is of major importance to understand the exact molecular basis of its operation.

There are many examples of how an understanding of the molecular basis of contractility is relevant to the understanding and control of such diverse phenomena as myocardial contractility, arterial smooth muscle tension, and clot retraction by platelets. Relaxation in all of these systems apparently occurs when certain key steps in the contractile cycle are blocked. However, modulation of other steps is also undoubtedly crucial. Relaxation is not an all-or-none process; beat regulation in cardiac muscle and tension regulation in arterial smooth muscle must all be modulated through changes in the rates of steps in the contractile cycle. Clearly, intelligent control of these phenomena requires an understanding of their mechanism.

Muscle contraction and relaxation are subject to complex control systems of neurohumoral type. These messengers and their receptors are in turn subject to other reflex and physiological feed-back control systems. Such systems expressed through actin-myosin interactions provide automatic and voluntary control of muscle movements.

In disease states, either the actin-myosin properties or the control mechanisms may be disordered. For example, certain muscular dystrophies that affect both skeletal and cardiac muscle cells appear to be due to cellular disorders. In diabetes with neuropathic changes, some of the reflex control of cardiac function is lost. Perhaps this provides a clue to the high prevalence of sudden cardiac death in diabetics. The beating of the heart is a pumping cycle of relaxation for filling and contraction for ejection of blood. The ejection represents the output of the circulation. Ejection disorders are often due to loss of heart muscle (myocardial infarction), but in some circumstances, they result from molecular disorders of muscle cell contractile function. It has been observed that in chronic congestive heart failure, there is a progressive loss of beta-receptors from the muscle cells.

Blood pressure depends strongly on the degree of contraction or relaxation of the small arteries that distribute blood to the capillaries. Their tone sets the average blood pressure, which may then be raised or lowered by further contraction or relaxation. With the establishment of chronic hypertension, this capacity to adjust by relaxation may be seriously reduced. Orthostatic hypotension, which is a common problem of the elderly and a problem with some antihypertensive treatment, is the occurrence of low blood pressure on standing up. It may result in dizziness and fainting. It is a problem of excessive vascular muscle relaxation and pooling of blood in the legs. There is also arterial spasm. This is a condition of special clinical interest when it affects cerebral or coronary vessels. Segmental portions of these vessels may contract markedly and maintain contraction for many minutes producing angina or headache and perhaps precipitating thrombotic arterial occlusion with damage to the heart or brain.

Another example of the importance of understanding the basic contractile mechanism is its relationship to the velocity of heart muscle contraction. Several investigators have shown that thyrotoxicosis leads to a change in the dominant isoenzyme of myosin present in heart muscle, and this will be expected to influence the energy available for contraction. It may be that the effect of thyrotoxicosis on the velocity of heart muscle contraction is directly related to changes in the rates of specific steps in the contractile cycle. Understanding this cycle may enable the development of better mechanisms to control the velocity of heart muscle contraction.

- Hemoglobin Switching: A Model for Study of Gene Regulation During Development and Cellular Differentiation

The remarkable explosion in knowledge about globin gene structure and function provided by molecular biological-recombinant DNA technology has offered a unique opportunity to understand disease mechanisms and to develop novel approaches to therapy. Systematic investigation of the thalassemic disorders has resulted in a more complete understanding of the mechanism of this disease. Restriction endonuclease

mapping studies and definition of specific nucleotide substitutions that alter gene function have provided the means to recognize mutations in fetal DNA, thereby affording a method for accurate prenatal diagnosis of these syndromes.

The thalassemias and hemoglobinopathies also serve as a prototype for the investigation of genetic disease. Extension of the techniques of molecular cloning, restriction endonuclease mapping, and DNA sequencing promises the solution to both the molecular mechanism and prenatal diagnosis of any genetic disease. Equally as important as the understanding of specific molecular diseases are the mechanisms by which individual genes are regulated during development and cellular differentiation. The advanced state of knowledge about the hemoglobin genes combined with an understanding of the cellular processes of erythroid differentiation afford a unique opportunity to relate gene function to cellular differentiation.

All human disease, whether based on mutation in a specific gene or on complex interactions between an individual's genome and environment, has a genetic basis. By understanding genetic mechanisms, namely the means by which specific genes are turned on and off and the manner that alteration in DNA sequence affects gene function, knowledge of human disease can be greatly increased.

During development, there is a switch from fetal to adult hemoglobin synthesis. This switch occurs during the perinatal period when the gamma globin genes are turned off and expression of the beta globin genes increases dramatically. Thus, a major change in the phenotype of red cells--namely the nature of their hemoglobin--reflects regulated expression of the genes within a specific gene family. The phenomenon of hemoglobin switching can serve as a prototype for investigation of gene function during cellular differentiation and the development of an individual.

Systematic examination of individuals with an altered pattern of fetal and adult hemoglobin production has suggested many genetic mechanisms that may influence globin gene expression, although the molecular basis of these mechanisms is not yet known. The thalassemia mutations decrease adult hemoglobin production and are accompanied by an increased production of fetal hemoglobin. Analysis of these mutations has suggested the existence of DNA sequences remote from the globin genes themselves that nonetheless alter globin gene expression. Some of these mutations undoubtedly occur in the gamma globin genes themselves but others have been shown, by genetic analysis, to be unlinked to the globin gene family and perhaps to lie on chromosomes other than those that contain the globin genes. This evidence suggests that there are transacting factors, presumably proteins, that may alter gene expression and be susceptible to mutations that alter their function. These elusive regulatory molecules should be identified and characterized. The developmental regulation of hemoglobin production is of direct relevance to human disease, and the pharmacological manipulation of globin gene expression is a very

active area of investigation that will develop as new insights are obtained into the cellular and molecular basis of gene regulation. At present, the major areas of opportunity are:

Hematopoietic Stem Cells. Culture methods for primitive stem cells are inadequate. Only by developing the means to propagate these cells in the laboratory can their properties be defined and the nature of the molecular events that control globin gene expression be elucidated.

Hematopoietic Factors. Many factors such as erythropoietin are essential for differentiation of hematopoietic cells. These factors must be purified and obtained in adequate quantities to allow their effects on purified stem cells to be defined.

Genetic Regulatory Molecules. Until now the powerful recombinant DNA molecular cloning methodology has been largely applied to defining gene structure and relating primary structure to function. The opportunity now exists for exploitation of this methodology to define intracellular regulatory factors and to identify the genes for these factors.

Genetic Interactions. The combination of extensive knowledge of globin gene organization and structure and of the evidence that remote genetic loci influence their function provides a unique model to approach genetic interactions. These modifying loci should be identified and their mechanism of action elucidated for the insights these studies will offer into hemoglobin switching. They are also likely to be prototypical for other complex genetic interactions.

- Endothelium

The ability to cultivate and collect endothelial cells in large numbers and to subject them to exquisitely sensitive and specific modern biochemical and biophysical analyses has provided hypotheses that were inconceivable as little as a decade ago.

Previous studies of biochemical properties were limited to vascular strips until endothelial cells were successfully cultured free of other cell types a decade ago. Since that time, a large body of knowledge has accumulated on the metabolism of these cells and their interaction with a variety of natural and synthetic compounds, including proteins, cells, and drugs. Several laboratories have now reported success culturing endothelium from a variety of adult human vascular beds, and the information on endothelial cell properties should expand significantly.

Research opportunities include characterization of the unique qualities of the pulmonary epithelium, elucidation of the role of the epithelium in thrombosis and hemostasis, and determination of the details of the mechanisms of atherogenesis affected by endothelial

cells. More general studies should include establishment of correlates of animal or juvenile cell model systems to adult human physiology in vivo; and study of the variations in cellular functions with growth cycle, crowding, and influence of other cell types, and in various pathologic conditions.

Role of the Endothelium in Atherogenesis and Coronary Heart Disease

The endothelium of the large arteries covers a relatively small area, and unlike lung endothelium, it cannot act as a metabolic organ influencing systemic metabolism. Its behavior as a selectively permeable membrane does not involve major fluxes, the effect being limited to exchanges of local tissue interest. These local phenomena are of critical importance to pathological events that express themselves as atherogenesis, arterial thrombosis, and arterial vasomotion (spasm or relaxation). Evidence has recently appeared that the endothelium may have a role in vasomotion. Such observations generate numerous questions about that role and also opportunities to investigate vascular spasm. In addition, findings based largely on bovine aortic cells and on experiments in vivo in animal models point to major ways in which endothelium has a role in atherogenesis.

There is a turnover of arterial endothelial cells with loss of individual cells, and the replacement of these cells and the restoration of membrane integrity is a critical matter. It appears that the loss of single cells is almost immediately restored by cell movement and subsequent multiplication. Nevertheless, cell turnover is highest at sites of predilection for atherosclerosis and the reason for this is not known.

The atherosclerotic plaque is a space-occupying lesion composed of a proliferation of smooth muscle cells, an accumulation of monocytes-macrophages, matrix proteins in large amounts, lipids, blood coagulation or thrombotic products, and endothelium. It exists in arteries capable of vascular tone, vasomotion, and spasm. The endothelium can be postulated to affect all of these plaque properties, and numerous opportunities exist to derive new information about them.

The Pulmonary Endothelium

New research methods have increased the understanding of the sub-cellular mechanisms by which pulmonary endothelial cells selectively process circulating substances. In vitro studies have provided direct evidence that they perform a wide range of metabolic activities. Other work has revealed that some compounds are synthesized or inactivated on the luminal surfaces of endothelial cells, others are metabolized intracellularly; and still others pass through the pulmonary circulation unaffected. Neither the physiological significance nor the clinical implication of these metabolic activities are fully understood. Pulmonary endothelial cells, for example, appear to play an important role in the renin-angiotensin system. They contain a number of enzymes capable of metabolizing angiotensin and

bradykinin. The angiotensin-converting enzyme determines, to a large extent, the amounts of angiotensin II (a potent vasoconstrictor) and bradykinin (a potent vasodilator) entering the systemic circulation. In addition, several vasoactive agents are inactivated or released by the lung into the arterial circulation. The lung therefore may play a role in controlling blood pressure.

In the study of cell-to-cell interactions, it was recently discovered that acetylcholine (ACh)-induced relaxation of systemic and pulmonary vascular smooth muscle is dependent on the presence of an intact endothelial lining. The physiological significance of endothelial mediators in modifying vascular smooth muscle tone is enormous. In the lung, for example, a better understanding of the mechanism of induced smooth muscle relaxation may provide new approaches to the treatment of primary pulmonary hypertension.

Hemostatic Properties of Endothelial Cells

The endothelium represents the interface between metabolically and mechanically active solid tissue and the fluid blood transport medium. The blood must supply nutrients and oxygen to the tissues and remove the metabolic products. The endothelium fulfills an important active as well as passive transport mechanism for these materials. In order to be effective, however, the endothelium and blood components must not interact in such a way as to block transport. It is now clear that the endothelial cell has an active capacity for maintaining blood fluidity.

It is also known that endothelial cells have some thromboplastic activity if they are injured and can presumably initiate coagulation. However, the cells also respond to thrombin by generating activities that will eventually inhibit coagulation. The endothelium does not normally react with platelets, but may do so if injured or transformed. The endothelial cell also actively produces and processes von Willebrand's factor (factor VIII antigen) which is essential for platelet adhesion and aggregation that is initiated by collagen. A particularly interesting feature of endothelial metabolism is that vascular endothelial cells produce several plasminogen activators, and also their inhibitors. Thus endothelium has a role in fibrinolysis. This characteristic might lead to new approaches to therapy for thrombosis. Work on understanding the interplay of inflammation with hemostasis at the endothelial interface is only in its infancy and warrants intensive investigation.

● Free Radical Injury

Oxygen toxicity affects to some degree the enzymatic processes of every living human cell, and it may be active in some tissue components even when air is breathed at atmospheric pressure. It now appears that singlet oxygen, superoxide anion, hydroxyl radical, and

hydrogen peroxide involve oxygen species participating in free-radical chain reactions that stimulate three different but simultaneous events: (1) the primary response at the molecular level; (2) defense mechanisms that normally oppose their action to the initial injury; and (3) failure of enzyme, cell, or tissue to show their normal properties or to perform their physiologic function. Understanding all these manifestations of oxygen toxicity is essential to development of effective measures or agents to counter the destructive process that is thought to be characteristic of many pathological changes.

The free radical theory of oxygen toxicity attributes the damaging effects of hyperoxia to highly reactive metabolic products of oxygen that can inactivate enzymes in the cell, damage DNA, and destroy lipid membranes. Opportunities now exist to understand the molecular mechanisms of oxygen toxicity and of the endogenous defenses that organisms have evolved against oxygen free radical injury. This research may not only lead to a more rational basis for the clinical use of oxygen but may identify an important link in the processes of cellular injury that can culminate in edema, hemorrhage, and hyaline membrane formation and fibrosis in the lung, and contribute to the pathogenesis of atherosclerotic plaques.

An adequate supply of molecular oxygen and its appropriate use are critically important factors in most biological systems, including those of the normal and ill person. Oxygen depletion is extraordinarily common and affects patients with a wide variety of disorders, including diseases of the lung and heart, and circulatory, hematologic, neural, and neuromuscular systems. However, abnormally high as well as abnormally low oxygen concentrations produce distortions of cell and organ function. Here, the lung is of pivotal importance because it is the portal of entry for high oxygen concentrations. Much of the current research on lung tissue related to the cellular, biochemical, and molecular changes produced by high oxygen exposures provides an excellent basis for understanding many diverse biological systems similarly exposed.

The mechanisms of oxygen toxicity at the molecular level are now generally attributed to reactions of oxygen-free radicals with cellular components. These oxygen-free radicals are products of normal cellular oxidation-reduction processes; under conditions of hyperoxia, their production increases. These short-lived species are capable of various toxic activities including inactivation (oxidation) of sulfhydryl enzymes, interactions with DNA and lipid peroxidation of cellular membranes. One of the common pathways leading to injury is through the formation of malondialdehyde. Another may be through the generation of intense destructive heat within very localized domains.

A large amount of evidence has appeared in the past decade about the endogenous defense systems that protect the biological integrity of the organism from oxygen-free radical destruction, and these include

antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), lipid membrane soluble constituents (vitamin E), and other intracellular antioxidant compounds (ascorbate, glutathione). Research on the mechanisms of cellular defenses against toxic species of oxygen is providing interesting new results.

A problem that has been perplexing investigators of oxygen toxicity for years has been why the pulmonary endothelium is more vulnerable than the alveolar epithelium to hyperoxic lung damage, since the latter is also directly exposed to the high oxygen tensions of alveolar gas. Researchers now theorize that some blood or blood cell-endothelial cell interaction may occur that multiplies the toxic attack on the endothelium. Since platelets also are known to release oxygen radicals during clumping and metamorphosis, the attachment of platelets and release of their contents to oxygen-damaged endothelial cells may result in an exacerbation of oxygen radical attack. This process could accelerate the destruction of the endothelium that occurs in pulmonary oxygen toxicity, and this initiates the cascade of pulmonary edema and hemorrhage that can result in pulmonary fibrosis or death.

Free radicals have also been postulated to affect atherogenesis. In the early stages of plaque formation, monocyte-macrophages gather in the lesion in considerable numbers. They may also be accompanied by small numbers of polymorphonuclear leukocytes. As these cells engage in lipid accumulation and scavenging, they are thought to generate oxidative free radicals, which may influence atherogenesis in several ways. Cellular toxicity from malondialdehyde formation, heat, or other actions may kill cells and contribute to the cellular necrosis that is an important aspect of early plaque formation. It may also contribute to the necrosis that occurs at the margins of mature pultaceous atheroma. It is known that oxidative products of cholesterol are cytotoxic to arterial cells in vitro and in vivo. The formation of such products in situ by simple oxidation or by free radical formation may be a further means of promoting the vascular injury and repair reactions characteristic of atherogenesis. It should also be noted that plaques often contain ceroid. Ceroid is a varnish-like brown pigment that is highly insoluble and is probably derived from the oxidation of polyunsaturated fatty acids in situ. Its formation may be another indication of free radical activity in atherosclerosis.

- Blood Resources: Transfusion Medicine

Numerous opportunities for scientific research exist in transfusion medicine, such as the development of new blood products prepared through fractionation techniques or recombinant DNA technology, development of methods to improve and assure the stability and safety of these products, identification of clinical conditions that will benefit from transfusion therapy, and development of procedures to improve the safety of transfusion. The following brief summaries offer examples of some of the challenges facing investigators in the area of transfusion medicine.

Research is needed to develop methods to separate neocytes (young red cells), efficiently and economically, from mixed populations of red cells for use in chronic transfusion programs. Similarly, there is a need to develop methods for the collection, separation, and preservation of stem cells from peripheral blood for bone marrow transplantation. Development of methods to improve bone marrow transplantation is also an active area of study. The identification, isolation, and, characterization of the viruses of non-A, non-B hepatitis, the primary cause of transfusion-transmitted hepatitis, also remain major goals. In addition, if an infectious agent is identified in the etiology of AIDS and its transmission by blood products is established conclusively, methods will be needed to identify the carrier state and to inactivate the agent or remove it from blood and blood products.

More than 100 proteins are known to be present in plasma. Only 10 percent of these proteins, however, have been sufficiently characterized or isolated for clinical use. Thus, a substantial number of potentially useful plasma proteins exist, and research is needed to identify and evaluate the most promising candidates for clinical use. The management of bleeding disorders offers added opportunities for research. Platelet alloimmunization may be due to platelet-specific antigens or HLA antigens. The problems of platelet immunology as they apply to the selection of compatible donors for transfusion have been only partially resolved, and more information is needed. Immunological investigations are also important in examining the relationship between transfusion and success in organ transplantation.

The technique of therapeutic apheresis is being applied to many diverse clinical conditions, but very little is known about the clinical efficacy or cost-benefit of its use in many of these situations. Controlled clinical studies in this area of transfusion medicine are therefore necessary to provide the basis of a more rational use of the method with patients who can be expected to receive positive benefit from its application.

In 1979, the number of Americans from whom whole blood or blood components was collected approached 6 million. In the same year, 2.9 million patients received whole blood or red cells, or both, as part of their therapy. In all, nearly two dozen types of blood products are transfused to patients. New technologies of blood preservation and blood collection have in the past few years made therapeutic approaches possible that were previously unheard of, and the importance of blood transfusions has been greatly increased through the use of components in increasingly specialized and effective forms of therapy.

The number of plasma derivatives available to the public remains small compared with the number that may be clinically useful. Within the last 15 years, only one new plasma derivative, antiinhibitor coagulant complex, has been introduced into clinical practice. This

product is currently being used for the treatment of bleeding episodes in patients with hemophilia A whose course is complicated by antibodies to factor VIII even though there has been limited clinical investigation to prove its effectiveness. There have been few clinical studies of other recently identified plasma derivatives (anti-thrombin III; C1-inactivator; fibronectin; alpha-1-antitrypsin) and almost none of the derivatives that have little commercial potential (orphan products) but that may be significant for treatment of rare disorders. Consequently, knowledge about blood and plasma acquired during the past 30 years has been transferred to patient care at a slow pace. Newer treatment regimens, such as therapeutic apheresis, have not been adequately evaluated in a controlled clinical setting. A lack of programs to assess the safety and efficacy of new or improved blood products and therapies is thus a major problem in the field of transfusion medicine.

One of the most important challenges in the area of plasma derivatives is related to developing new protein separation techniques to isolate, purify, and prepare safe products for research and therapeutic use. Methods, such as those based upon hybridoma or recombinant DNA technology, for producing some of the most frequently used plasma constituents without reliance on plasma as the source material are being developed and could be applied to an even broader range of plasma proteins. Once these newer materials are available, their clinical efficacy relative to material separated from plasma must be established.

NATIONAL INSTITUTE OF NEUROLOGICAL AND
COMMUNICATIVE DISORDERS AND STROKE

I. Major Program Changes, FY 1986

● Biological Basis Research

The NINCDS plans to undertake the following initiatives and new activities in FY 1986:

- Huntington's Disease: Studies to pinpoint the defective gene will intensify now that the gene marker has been identified. Discovery of the actual gene will allow us to examine how the mutant gene produces its deleterious effects.
- Alzheimer's Disease: The role of inheritance and other risk factors will be studied in families in which Alzheimer's disease occurs frequently. Powerful new molecular technologies will be used to study the cause and progression and perhaps to aid in the diagnosis of this disease. Scientists will map chemical changes in the neurotransmitter systems in various regions of the brain. The metabolic alteration of particular cell types will also be investigated.
- Neuroimmunology: Research will be accelerated on the role of the central nervous system on immunological reactivity of the body. We will study the physiological function of the immune system organs, the lymph nodes, spleen and thymus, as well as innervated bone marrow.
- Monoclonal Antibodies: Scientists will apply monoclonal antibody techniques to provide additional antibodies which bind specifically to neurotransmitter receptors. They will attempt to localize receptors in nerve tissue at an ultrastructural level and to identify receptor deficits in a variety of neurological diseases.
- Memory and Learning: Research will continue on the physiological and biochemical events associated with memory and learning. We will investigate the synthesis of specific proteins controlled by the genetic apparatus of the cell.
- Neurotransmitters: Research will emphasize substances such as peptides and amino acids or "co-transmitters" which modify synaptic activity. We will try to discover how membranes bind neurotransmitters.
- Speech and language: Recent studies have shown that a number of common disorders including dyslexia and language-learning difficulties may have a genetic basis. Chromosomal studies of normal subjects and individuals with speech and language handicaps are planned.

- Brain Blood Flow: The discovery that the brain regulates its own blood flow without altering metabolism has helped us understand the brain's circulatory system and metabolism. The NINCDS hopes to sponsor studies of the anatomical, physiological and neuro-chemical aspects of brain circulation so that we can better understand how to circumvent malfunctions.
- Clinical Research
 - Imaging technologies: The NINCDS will emphasize the further development of the emerging brain imaging technologies, positron emission tomography (PET) and nuclear magnetic resonance (NMR) spectroscopy. These technologies permit the first noninvasive attempts to correlate brain dysfunction and other disorders with structural or functional changes. For example, they plan to study the lesions which occur in tuberous sclerosis and neuro-fibromatosis to detect subtle changes in brain function.
 - Multiple Sclerosis: The search for drugs that may modify the abnormal immune response in MS will continue. Medications that show promise for the treatment of MS will be investigated, and efforts to minimize or eliminate the side effects and risks of these drugs will accelerate.
 - Neural Prostheses: While much NINCDS-sponsored research attempts to avoid the paralysis that results from spinal cord injuries, in many cases the paralysis and other effects do occur. The NINCDS is working to develop synthetic and biological prostheses to bridge the damaged peripheral nerves. We plan to test such bridges thoroughly for efficacy and for compatibility with the damaged and the existing surrounding tissues. Efforts to complete a neural prosthesis for upper limb movement in quadriplegics will be accelerated. Continued work on prostheses for the neurogenic bladder is planned.
 - Stroke: Concentrated research on the etiology, prevention, neuropathology, treatment, and rehabilitation of stroke is planned in the Stroke Research Centers and in individual research project grants. For example, PET will be used to monitor pathophysiological changes in the brain and to improve our understanding of different types of stroke. The effects of prostaglandins on platelet activity in the management of strokes and transient ischemic attacks will be studied.
 - Prescriptive System for Communicative Disorders: The NINCDS is encouraging investigators to develop a prescriptive system that will enable a close match to be made between the residual communication skills of the speech-handicapped individuals and state-of-the-art electronic speech production devices.
 - Head injuries: The major phase of a controlled study of intensive barbiturate therapy for patients with severe head injuries will begin.

- Intramural Research

- Brain Imaging: NINCDS intramural scientists will use PET to uncover the metabolic consequences of neuronal degeneration, cerebral blood flow interruption, and drug action in the human central nervous system. NMR techniques will be applied to localize the structural brain abnormalities to a degree not previously possible. The development and use of higher resolution scanners will be accelerated, as will the design of novel radioisotopic tracers. These efforts will provide a new, improved approach to study certain neuronal functions.
- Molecular Genetics: Seeking to understand the chemical basis of many neurological disorders, scientists in the NINCDS Intramural Research Program will examine the molecular events involved in duplication and expression of animal and viral chromosomes. Intensive research will be conducted on the myelin basic protein gene of the mouse chromosome, recently cloned by an NINCDS intramural scientist, in the hope that this knowledge may improve our understanding of MS. Other investigators will attempt to refine and test techniques for enzyme replacement, developed by NINCDS scientists, for Gaucher's disease and to develop similar strategies for the other lipid storage diseases, including Tay-Sachs and Niemann-Pick diseases.
- Communicative Disorders: Multidisciplinary intramural studies of inner ear structures and mechanisms, including sensory cells and neurons and their interactions will provide new knowledge on the poorly understood mechanisms of hearing. We hope to achieve a better understanding of the causes of sensory deafness and nerve deafness. NINCDS scientists will also concentrate on neurotransmitter studies of how sound waves are conducted to and interpreted by the brain.
- Clinical Studies: Scientists in the NINCDS intramural program will attempt to develop improved drug therapies for a wide range of rare nervous system disorders. Particular attention will be given to drugs for the prevention and control of the convulsive disorders, Parkinson's disease, Tourette's syndrome, Huntington's disease, and Alzheimer's disease.
- Neurovirology: Investigators will concentrate on the ability of certain viruses to induce brain tumors and on attempts to modify the growth of these neoplasms. NINCDS scientists will attempt to define the regulation and replication of viruses which cause neurological diseases. For example, they will investigate the factors which permit certain viruses to attack the nervous system and to evade the neuroimmunological defenses of the host.

II. Areas of Scientific Opportunity

● Molecular and Cellular Neurobiology

Our basic knowledge of the neurosciences has increased dramatically in the past decade. There is a new, sharper understanding of the functionings of the brain and nervous systems in health and in disease.

While most research in the neurosciences may be considered neurobiology, this term is usually applied to investigations at molecular and cellular levels, to comparative neuroanatomy and neurophysiology, to the study of model systems such as tissue culture, and to the basic functioning of the human brain and nervous system. Neurophysiological studies have documented the functional interrelationships among cells, identified "command neurons," and the specific responses to discrete stimulation, movement of specific muscle groups, or other integrated complex behaviors. Appropriate neurochemical studies have identified the diverse neurotransmitters involved in synaptic transmission.

Among the many rapidly advancing research areas in neurobiology, the following offer exciting scientific opportunities. These are:

●● Neurotransmitters

Nerves communicate with each other and with muscles, glands, and other tissues by means of neurotransmitters. These substances, released at the nerve endings, bind to receptors on the surfaces of adjacent nerves or muscles and initiate electrical activity. Some well-known neurotransmitters, including acetylcholine, dopamine, norepinephrine, gamma amino butyric acid, and serotonin, have been studied for decades. Others, such as the amino acids glutamate and glycine, have recently gained prominence. In recent years investigators have identified peptides that may be neurotransmitters, co-transmitters, or neuromodulators; these peptides appear to have a significant but as yet undefined role in neurotransmission. The attempt to discover more neurotransmitters continues using time honored methods for isolating biologically active substances and the more recent methods of molecular genetics.

Several neurological and psychiatric diseases are characterized by the loss of cells that produce specific neurotransmitters. For example, in Parkinson's disease, dopamine is deficient. In Huntington's disease, gamma amino butyric acid may be in short supply. Alzheimer patients suffer from a deficiency of acetylcholine, while depression may result from an imbalance of norepinephrine and serotonin.

Additional effort needs to be dedicated to the biochemistry, physiology, and pharmacology of neurotransmitters. The areas that require additional study include biosynthesis from precursor molecules, the storage of neurotransmitters, the physiological

and biochemical processes associated with release, the chemistry and pharmacology of the receptor, and finally the many processes associated with removal of the neurotransmitter after the receptor is activated.

The new imaging techniques, particularly positron emission tomography (PET), have enhanced our understanding of the workings of neurotransmitters and may help in the search to identify additional neurotransmitters. PET is revealing metabolic patterns of regional neuronal activity that take place in the brain during normal activities such as speaking, hearing, and thinking and is beginning to show the sites of neuronal malfunction associated with Alzheimer's disease. PET may, for example, show where a particular neurotransmitter actually is congregated in the brain.

●● Receptors

Receptors receive neurotransmitters and, in a sense, are their functional sites. Receptors are particular parts of proteins that are imbedded in the membrane of the nerve cells which pick up the neurotransmitter when it is introduced into the synapse between nerve cells. Each neurotransmitter has a unique receptor; thus, there are many types of receptors. The receptor for acetylcholine is best understood. It is composed of five subunits of protein. The genes that are the code for the acetylcholine receptor are now also known and this receptor has been cloned. Scientists are duplicating the acetylcholine receptor clone and studying its molecular organization.

Many diseases are caused by receptor malfunctions. When this occurs, the neurotransmitter-receptor link is not completed and the nerve communication does not take place. Parkinson's disease is one example of a disorder related to receptor dysfunction; in this disease as well as there being a shortage of the neurotransmitter dopamine, the receptor to dopamine malfunctions. Another disorder in this class is myasthenia gravis. In this disease the immune system appears to destroy the nerve receptor.

The search for new neurotransmitters often includes the search for matching receptors to increase our understanding of the nerve communication process. This knowledge is crucial to an understanding of specific receptor-related diseases. If we can understand what the receptor is and how it functions, we will be well on the way to designing specific therapies for specific diseases. These chemicals may be able to take the place of the receptor that is not functioning normally.

●● Trophic Factors such as Nerve Growth Factor

Trophic factors can be thought of as those proteins that nourish the nerve cell. Several different trophic factors have been identified.

Nerve growth factor (NGF) is the best known trophic factor. It is a neuropeptide protein that is important in the development of the nervous system and in the maintenance of neurons. While its exact mechanism of function is not fully understood, it is believed that nerve growth factor and other similar materials are the chemical method by which nervous connections are made in the nervous system. There is increasing evidence that the growth of nerve endings is a natural process. A significant amount of nerve growth factor has been found in the salivary glands, where there is a concentration of nerve fibers. Nerve growth factor has been a valuable source of knowledge into the developmental biology of the peripheral nervous system. It has been crucial in identifying other polypeptide growth factors.

We now know that nerve growth factor is taken up by nerve endings. Nerve growth factor has also stimulated research on neurotrophic factors which may be important in treating various neurological disorders. A nerve growth factor gene has recently been cloned. This accomplishment will allow the role of nerve growth factor to be fully investigated and its potential value in therapies for neurological disorders to be studied. For example, the natural function of nerve growth factor, now unclear, can be studied in detail. The role that this substance takes in stimulating nerves can also be investigated. Scientists may someday discover that nerve growth factor has clinical implications, perhaps in helping damaged nerves grow back and, even, in treating paralysis.

The hypothesis that Alzheimer's disease is caused by a shortage of neurotrophic factors is now under active investigation. The neurotrophic hormone keeps the cortical tissue healthy; without this hormone, the nerve cells wither and die and may be the cause of the disease. If this hypothesis proves true, it may be possible to design a therapy for Alzheimer's disease in its early stages.

Increasing our knowledge of neurotransmitters and receptors may enable us to develop therapeutic models as well as clinical therapies for several currently untreatable neurological diseases. This opportunity will result from a better understanding of the various basic processes involved in neurotransmitter production, release, receptor activation, and removal. For example, patients with Parkinson's disease are given L-Dopa, a precursor of brain dopamine. By extending the same principle, choline for Alzheimer patients may possibly result in higher brain levels of acetylcholine. Similarly, myasthenia gravis patients suffer loss of acetylcholine receptors on muscle, so that cholinesterase inhibitors prolong the activity of released acetylcholine at the neuromuscular junction. Depressed patients are provided drugs that delay the removal of dopamine and norepinephrine from the synaptic cleft. Continued basic and clinical research, augmenting current knowledge of neurotransmitters function, should have a significant impact on the treatment of several prominent incapacitating neurological diseases.

- Neurogenetics

Research on neurological diseases is greatly aided by knowing that a disorder is caused by the derangement of a gene or genes. Research strategies such as genetic linkage and somatic cell genetics can be used to try to localize the defective gene on a chromosome, isolate the gene, sequence it, identify the defect, and develop a treatment or prevention technique.

There are presently 3,368 known genetic diseases with over 900 single gene disorders affecting the nervous system. To date, less than 40 of these neurological disorders have been linked to a particular chromosome. Our capacity to map genes to specific chromosomes has been hampered by the limited availability of polymorphic markers.

Recombinant DNA methodology provides an alternate--and more powerful--strategy for developing plentiful polymorphic markers for linkage analysis. Recombinant DNA techniques make it possible to detect polymorphism in DNA sequences directly, without looking for its expression as eye color or enzyme levels. These polymorphic DNA sequences can be used as genetic markers in linkage studies and can substantially increase the number of markers available.

Following are three important examples of neurogenetic research conducted or supported by the NINCDS:

- Gene Marker for Huntington's Disease

In October 1983, scientists, funded by NINCDS, announced that they had discovered a genetic marker for Huntington's disease. This exciting and important discovery promises to allow early diagnosis of the disease for many Huntington's disease families. Eventually the discovery should lead the way to prenatal diagnosis and perhaps therapy.

The scientists arrived at the finding through several techniques. They constructed a family tree of a hundred year old Venezuelan family and of American Huntington's disease families. Tissue samples of healthy and ill members of these Huntington's families played a crucial part in the discovery. The scientists used recombinant DNA techniques, gene splicing, to examine the genes in the tissue samples. The marker discovery is exciting not only because it promises to produce an early and reliable diagnostic test for this dread disease, but also because the Huntington's gene itself is believed to be very close to the disease marker. The search for the gene will now be accelerated and the gene-contributed defect that causes Huntington's disease may soon be unearthed. When it is, scientists may begin to devise therapies for the disease and, possibly, ways to prevent its clinical occurrence.

●● Programmed Cell Death

The concept of programmed cell death is that a gene or some other factor causes the cell to wither and die prematurely. It is possible to postulate many causes for programmed cell death. A gene defect might be to blame, causing a shortage of some material necessary to the cell or an excess of a material that is harmful to it. Still another potential reason for programmed cell death might be a slow virus, as in Jakob-Creutzfeldt disease or in kuru.

Programmed cell death may be caused by different factors and appear in different parts of the central nervous system depending on the disease. At the present time, it seems to occur in several different diseases. For example, in Alzheimer's disease, specific nerve cells of the cerebral cortex die; in Huntington's disease, it is specific nerve cells in the basal ganglia that die; in ALS, the motor neurons of the spinal cord and brain; and in Parkinson's disease, the substantia nigra. As scientists have long been aware, these cells seem to function perfectly in early life but die later on. The "programming" may occur early in life, but the actual damage occurs much later. This programmed cell death is not, with our current knowledge, reversible.

●● Storage Diseases and Enzyme Replacement

Gaucher's disease, Tay-Sachs disease, Niemann-Pick disease, and Fabry's disease are known as the lipid storage diseases. Each is hereditary. As a result of enzyme deficiencies, a dangerous build-up of fatty compounds occurs in the brain and body cells of patients with these diseases.

NINCDS intramural and extramural scientists are conducting major studies into these lipid storage disease. Enzyme replacement for these diseases has progressed from a hope to an actual, if experimental, therapy. The specific enzyme defect in each disease is now known. In Gaucher's disease, enzyme replacement is now successful in several stages of the disease. Current NINCDS intramural research focuses on two aspects of these genetic disorders. The first is to determine the molecular basis of these metabolic defects. An extraordinarily important clinical application has already resulted from studies on glucocerebrosidase isozymes in tissues of Gaucher patients. Moreover, a procedure has been developed that permits discrimination between the neuro-pathic and non-neuropathic phenotypes of this disorder. These discoveries are very important for precise genetic counseling and for developing the correct strategy to treat patients with different clinical phenotypes.

The second aspect of NINCDS research addresses the potential of enzyme replacement for the treatment of patients with Gaucher's disease. The requisite enzymes for Gaucher's disease have been isolated in homogeneous form from human placental tissue. Encouraging responses have been obtained in certain young patients

with Gaucher's disease who received the enzyme. Their general health and vigor are improved; the progression of spleen enlargement has been arrested; and their platelet levels have stabilized. All eight recipients have not required splenectomy.

Scientists are now attempting to develop an enzyme replacement therapy that will both cross the blood-brain barrier and reach the proper area of the brain, thus aiding children and adults who have neurological involvement.

The broad field of neurogenetics offers a wealth of scientific opportunities ripe for investigation. In particular, molecular genetics provide a valuable strategy for understanding, treating, and eventually preventing neurogenetic disease. The methodology unifies a diverse field and applies generally to single gene diseases and possibly to multifactoral genetic illness. These new techniques represent a quantum advance in revealing the basic mechanisms of inherited diseases which afflict over 12 million Americans.

- CNS Regeneration and Implants

- CNS Injury and Regeneration

In addition to the damage incurred as a result of the initial injury to the brain or spinal cord, the central nervous system (CNS) undergoes secondary reactions that exacerbate the condition and cause irreversible damage. These include elevated pressure within the cranial or vertebral vaults, diminished blood flow, hypoxia, altered blood clotting, edema, changes in ionic concentrations, and modification of the neurochemical environment. Cells are killed or so badly damaged that they malfunction. Partial or complete paralysis may result.

When preventive or intensive therapy is unable to sustain normal function, additional therapeutic approaches become paramount. A multifaceted effort involves unraveling the factors contributing to regeneration and plasticity in the CNS. A number of recent studies have disclosed some of the specific factors that (1) insure neuronal survival, (2) promote the regrowth of nerve fibers, (3) attract regrowing axons, (4) provide a growth path for the extending axons, and (5) enable axons to make functional connections. Experimental models have established that there may be complete regeneration of nerve fibers in invertebrates following injury to the CNS, while in lower vertebrates repair is sufficient to establish sustained function. Mammals seemingly exhibit less potential for neural regeneration. Efforts are underway to define the internal milieu most conducive to effective neural repair. Investigators are evaluating the use of nerve tissue transplants to help bridge injured sites and to provide necessary neurotransmitters to restore normal function. In addition to these promising avenues of research to increase our understanding of the pathophysiology of CNS trauma and neural regeneration,

recent studies suggest the potential for significant improvements in the areas of diagnosis (e.g., evoked and spontaneous potentials), and long-term rehabilitation, including the utilization of neural prostheses.

●● Central Nervous System Implants

While the idea of implanting sections of central nervous system (CNS) into the brain was originally conceived at the turn of the century, recent experiments in CNS implants have raised the issue anew and made it a possibility as an effective treatment for spinal cord injury and for diseases such as Parkinson's disease and Alzheimer's disease. Recent research has been designed to provide more specific information about this possibility. Two categories of studies are underway: studies oriented toward mechanisms of development of the CNS and studies of methods to repair or replace damaged or nonfunctioning portions of the CNS.

Developmental studies using implants have focused on the classical questions addressed by experimental neuroembryologists. They ask: "What factors influence cell migration and differentiation? What guides axons to their final destination? What conditions are required for anatomical synapse formation and neurotransmitter production? How specific are the neuronal connections that have been established?" Some synapses seem to be highly specific in the connections made in the host brain, while other implants form more general synapses.

The second type of studies offer a promising method for restoring lost CNS function due to disease, injury or genetic disorder. This usually involves placing tissue adjacent to the nonfunctional or injured site in the host CNS and allowing it to develop. In several different animals, chromaffin transplants have been shown to alleviate functional disorders induced by lesions.

Swedish researchers have used a promising technique developed by an NINCDS grantee to implant adrenal medulla cells in several patients with Parkinson's disease. While the results to date have been mixed, the approach is very promising and scientists in several research centers are studying it.

Both CNS regeneration techniques and CNS implants aim to repair damaged or nonfunctioning central nervous system tissue. The social, emotional, and vocational consequences of CNS damage are incalculable. Recent advances in studies of CNS reactivity and plasticity indicate the appropriateness of intensifying the research effort to further understand CNS regeneration and implants in order to help prevent or ameliorate the consequences of CNS trauma and cell death. The new methods of implantation and the success of some of these attempts show that the time to study this approach has arrived.

- Immunology and the Central Nervous System

The brain is a "privileged" area immunologically in that the blood-brain barrier serves as a biological filter for cross immune reactions. Thus, neuroimmunology, the immunology of the nervous system poses very specific and unique research problems, problems which are being addressed by a specially trained cadre of neuroimmunologists. The application of immunological concepts is particularly promising in five areas of neuroscience research:

- Immunological uniqueness of the nervous system.

In some circumstances, immune reactions within the CNS seem to occur independently of the immune system outside the CNS. One reason for this may be the existence of the blood-brain barrier. Multiple sclerosis, CNS infections, and primary CNS neoplasms are disorders in which the immunological capacity of the nervous system appear to play a prominent role, both in pathogenesis and in outcome. The mechanisms responsible for the unique immunological aspects of the CNS are unknown and deserve serious study.

- Role of the CNS in modulating the immune response.

The nervous system may modulate the immune response directly through the autonomic nervous system or via neuropeptides or other transmitters. Though still in its infancy, elucidation of the relationship may be of great significance, and this can only now be adequately studied.

- Neurological diseases which are immune mediated.

Neurological diseases which are immune mediated include multiple sclerosis (MS) and myasthenia gravis (MG). Contemporary immunological tools and concepts offer new ways to study the pathogenesis of these disorders and rational approaches to therapy.

Research on T-cells has lately been very productive. Clones of various T-cell lines are being investigated for the role they may play in producing diseases, including MS and MG. Susceptibility to certain neurological diseases, such as MG and MS, is correlated with specific histocompatibility antigens. There is evidence that different combinations of these antigens may be associated with either a mild or severe course of MS. Neuro-immunoepidemiologic studies may disclose markers which will help predict the future course of these otherwise unpredictable diseases. Such prognostic information will be helpful in assessing the efficacy of the intervention.

The development of monoclonal antibodies which identify surface markers unique to various nervous system tumors may eventually lead to effective therapy.

●● Use of immunology to study the nervous system.

The central nervous system and the immune system have a number of similarities. Each is composed of cells with different functions which react to each other by releasing soluble factors known as mediators or transmitters. The mediators or transmitters in turn react with receptors on other cells. While still new, the marriage between immunology and neurobiology has already resulted in the production of monoclonal antibodies which can distinguish a number of specific cellular components of the nervous system. Monoclonal antibodies directed at some of the neuromediators or transmitters are being used to assay these substances in the normal and diseased nervous system. Monoclonal antibodies have also been produced against some receptors for transmitters. In time, neuroscientists will have monoclonal antibodies directed against every subpopulation of cells in the nervous system, each neurotransmitter and its receptor. Undoubtedly, new transmitters and receptors will be identified during these investigations. They should permit extensive analysis of the nervous system in a manner not previously possible.

●● Neurological diseases due to infection.

In progressive multifocal leukoencephalopathy (PML), subacute sclerosing panencephalitis (SSPE), and MS, the immune response is probably abnormal. Immunology provides tools for studying infections of the CNS, understanding their pathogenesis, and generating therapies, e.g., interferon immune modulation or enhancement.

The scientific opportunities described here result from the dramatic increase in our understanding of general immunology and biology and the availability of powerful new technologies. The exploitation of these techniques may provide new insights into the understanding of normal and diseased nervous systems and promising techniques to prevent or arrest the course of chronic neurological diseases.

DIVISION OF RESEARCH RESOURCES

I. Major Program Changes, FY 1986

Expansion of capabilities in all program areas will be featured in 1986. A significant new endeavor will be the initiative in research facilities construction funding, to begin a program to construct needed institutional research facilities, and to provide for modernization or replacement of existing institutional research facilities.

● Clinical Research

Three new, small general clinical research centers are proposed which will emphasize outpatient research protocols. Six additional FTE's for the Clinical Associate Physician Program will add to the cadre of physicians trained in research. Sixteen new CLINFO awards will meet the needs of existing general clinical research centers for computer resources for clinical investigation. Further development of the CLINFO II system will explore methods of providing a nationwide clinical research information and data management system. CLINFO II will probably operate on microcomputers connected by a network, conceivably using one of the existing networks (e.g., Telenet, etc.), integrated with the present minicomputer hardware systems, and possibly connected to larger central computers.

● Biotechnology Research

Seventeen additional biotechnology resource centers will be funded to provide advanced instrumentation and up-to-date technologies for research investigators. Special emphasis will be given to new regional facilities for development and application of in vivo nuclear magnetic resonance (NMR) spectroscopy which is expected to serve the needs of both basic and clinical research scientists. In addition, centers for intermediate voltage electron microscopy and sophisticated image processing development and application will be available to investigators conducting research in cellular and molecular biology.

● Laboratory Animal Science and Primate Research

Five additional diagnostic laboratories will be located in areas presently not served adequately by existing facilities in order to provide for improved animal health programs, through appropriate surveillance activities and investigation of naturally occurring diseases and other problems of laboratory animals. These new laboratories will initiate studies on diseases of laboratory animals, elucidate new laboratory animal models of human disease, and develop resources for research and training including tissues, slides, and

photographs. To address the continuing shortage of veterinarians trained in laboratory animal sciences, support for 39 additional full-time training positions (FTTPs) is planned.

The Division's biological materials resources initiative will continue to provide coordination and support for a range of cell banks, tissue banks, human DNA probe banks, cellular materials repositories, and for related data bases of trans-NIH significance. Four such resources will be funded in 1986.

At the seven National Primate Research Centers the Division will continue facility repairs, renovations, and replacement of major fixed equipment. At other institutions receiving support through the NIH research project grant mechanism, thirty-five animal facility improvement awards will fund alterations and renovations necessary to upgrade the condition of research animal facilities.

- Biomedical Research Support Program

The Biomedical Research Support (BRS) Program will be increased substantially to compensate for inflation and to expand the ability of research intensive institutions to respond flexibly to the array of research needs that cannot be met through regular project grants.

Reflecting continued emphasis on meeting the backlog of accumulated research instrumentation needs, the Division intends to make approximately 40 additional Shared Instrumentation Grant awards.

Funding for the Minority High School Student Research Apprentice Program will be expanded to provide for an average of five students per participating institution, to allow for a "critical mass" of students within each program.

Within the BRS Program, a major new initiative will promote the development of top quality centers of biomedical research at historically minority institutions of higher education that grant doctoral degrees in, or related to, the health professions. The new program, entitled the Minority Graduate Center Development (MGCD) Program, will permit implementation of clearly defined plans for developing institutional potential for excellence in biomedical research. Initially, five awards are anticipated.

- Minority Biomedical Research Support Program

Building on the advice of the National Advisory Research Resources Council and other Division advisory groups, the Minority Biomedical Research Support (MBRS) Program has developed a number of new approaches to increasing the participation of minorities in biomedical research through graduate, four-year, and two-year minority institutions. In 1986, the MBRS Program will offer faculty research career enrichment awards, to provide faculty members off-campus research experiences at research-intensive laboratories for periods

of up to one year. It is expected that with support for continuing collaboration with scientists at host laboratories these research experiences will enhance and upgrade faculty skills and knowledge. In addition to the traditional MBRS awards, the MBRS Program will initiate seven thematic project awards. These awards will allow minority institutions to submit multiple applications, each addressing a focused area of research. The MBRS research instrumentation initiative at minority institutions will continue. Three additional traditional MBRS grant awards will be funded.

- Facilities Construction

A major initiative, which may require legislative authorization, will provide funds for research facilities construction. Such an initiative will allow the Division to begin a program to construct needed research facilities (animal facilities, toxic waste disposal facilities) and/or provide for modernization or replacement of existing research facilities at institutions conducting biomedical research. For example, many animal facilities serving NIH research programs have become obsolete and do not meet the optimum recommendations existing NIH guidelines. In some instances, the most cost effective way to improve these facilities is to replace them with new construction. This initiative will require no-year funds.

- Research Management and Support

The Division requires 10 new positions to carry out the program, review, support workload generated by the new or expanded extramural activities described above. In addition, the Division will acquire up-to-date equipment embodying recent advances in office automation technologies to conduct administrative and management activities most effectively and efficiently.

II. Areas of Scientific Opportunity

- Basic and Clinical Applications of Nuclear Magnetic Resonance

Atomic nuclei which are naturally present in human tissue, such as hydrogen, phosphorus and sodium, are magnetic and can be detected by the technique known as nuclear magnetic resonance (NMR). When placed in a magnetic field and excited by radio frequency waves such nuclei absorb and reemit radio frequencies characteristic of the particular nucleus and its environment. Since biological tissue is relatively transparent to radio waves and neither the radio frequencies nor the magnetic fields involved are known to pose health risks, this technique can be used to probe both anatomy and chemical events within organs and tissues.

NMR imaging of hydrogen nuclei in the body is an area of intense current interest in diagnostic medicine. The technique produces pictures comparable to those available from computed tomography (CT) scans which use X-rays, but the anatomical detail at least in brain

is better, and NMR scans seem to reveal tumors and other pathological conditions more effectively and earlier than CT scans. In addition, there is less risk to the patient. The physiological state of living tissue is reflected in cellular and organ metabolism. With suitable radio frequency coils, NMR can be used as a research tool to measure metabolism and changes in metabolism in vivo. Such studies have great potential for diagnosis of disease states, observing tissue metabolic alterations and the assessment of drug and other therapies in the elimination of abnormal metabolism and restoration of normal function. Phosphorus NMR has been used to study muscle energetics in healthy and diseased subjects, to monitor levels of adenosine triphosphate (ATP) as a measure of viability of human kidneys to be used for transplant surgery and to detect fatty deposits in arteries before they are evident from other means. The method provides measures of intracellular pH and levels of phosphocreatine, ATP and inorganic phosphate, so most aspects of cellular energetics (e.g. oxidative phosphorylation, glycolysis) can be studied. Carbon and fluorine isotopes can also be detected and should be valuable in studying metabolism and storage of isotopically enriched or labeled metabolites and drugs.

The Biotechnology Resources Program (BRP) has provided significant support for the development and use of high field NMR in biomedical research for many years. In view of the scientific opportunities provided through extension of the technique to include in vivo spectroscopy, the BRP has recently issued a Program Announcement inviting grant applications for support of regional facilities for development and application of in vivo NMR spectroscopy and new imaging methodologies. These facilities are expected to serve both basic and clinical research scientists and should greatly facilitate the creative application of these powerful new tools to biomedical research problems.

- Simian Acquired Immunodeficiency Syndrome (SAIDS)

A naturally occurring immunodeficiency syndrome (SAIDS) which causes high mortality in nonhuman primates is being studied.

Spontaneous outbreaks of immunodeficiency syndrome (SAIDS) have occurred during the past several years in macaque species (Macaca mulatta and Macaca cyclopis) at the California and New England Regional Primate Research Centers. A similar syndrome has occurred in another macaque species (Macaca nemestrina) at the University of Washington Regional Primate Research Center. The clinical manifestations in affected nonhuman primates, consistent immunological disorders, opportunistic infections, and other laboratory findings (pathological and serological) bear many similarities to those observed in human cases of AIDS. Immunological and pathological studies are currently in progress at these Centers. SAIDS has been experimentally transmitted with materials from affected animals to previously healthy macaques. Also, a type-D retrovirus has recently been implicated as a causative agent of SAIDS. These three Centers

have isolated, identified and characterized a type-D retrovirus from SAIDS-affected macaques in their colonies. In addition, the California Center has transmitted SAIDS with a laboratory culture of their type-D retrovirus. Efforts are continuing in the laboratories of these Centers and their collaborators to determine if these agent(s) are solely responsible for SAIDS and to define the method(s) of natural transmission.

As a result of intense investigations, the cause of human AIDS is believed to be HTLV III, a retrovirus similar in structure and biological effects to the SAIDS virus. The immunodeficiency syndrome observed in nonhuman primates (SAIDS) provides an excellent animal model system for basic studies on AIDS and the primate response to retroviruses. In addition, spontaneous immunodeficiency diseases pose significant threats in their own right to the maintenance of healthy colonies of nonhuman primates and must continue to be the subject of intense investigation. The nonhuman primate colonies of all seven Regional Primate Research Centers are being monitored for evidence of immuno-suppressive diseases.

Although not all scientists studying AIDS have fully accepted SAIDS as a valid model for studies on the human condition, it is apparent that there are a number of consistent similarities between these diseases and their causative agents. The isolation, identification and characterization of type D retroviruses from SAIDS-affected animals at three Centers, as well as the recent successful transmission of SAIDS with a type D retrovirus culture at the California Regional Primate Research Center, have created additional interest. These animals will be ideal subjects to aid in development of diagnostic and immunization methods. Several research projects on SAIDS have been funded by the categorical Institutes (NIAID, NINCDS, NHLBI). However, additional costs related to close surveillance of their primate colonies continue to be a financial burden on the base operating grants of the Primate Research Centers. Therefore, there is a need for funds similar to those requested in the AIDS-related supplemental FY 1984 appropriation. The usefulness of the nonhuman primate model has now been well demonstrated and continuation of this important and, to date, very successful research during the next two years is strongly urged.

- Lepromatous Leprosy Studies in Nonhuman Primates

Significant progress has been made by Primate Research Centers' scientists on experimental leprosy studies with nonhuman primates. A NIAID research grant and subsequent supplement for these studies were awarded to the Delta Regional Primate Research Center during the past year. These funds also provide partial support for an essential colony of leprosy-susceptible mangabey monkeys which are maintained and bred at the Yerkes Regional Primate Research Center. Since NIAID now supports a portion of this activity, the Primate Research Centers Program projects a slightly lower level of DRR funding for leprosy studies during FY 1984 and FY 1985 than was requested in last year's (FY 1985) request.

Collaborative studies between the Delta and Yerkes Regional Primate Research Centers and the Armed Forces Institute of Pathology for the characterization and establishment of nonhuman primates as animal models of human leprosy (Hansen's Disease) have continued during the past year. This work is now partially supported by a consortium grant awarded by NIAID.

Sooty mangabeys that were previously inoculated with Mycobacterium leprae, isolated either from a human source or from a spontaneous case of leprosy in a mangabey, have continued to show progression of this disease. These mangabeys, including the animal with the index leprosy case now undergoing treatment and six normal mangabeys have been studied to determine if alterations in immune parameters occur after M. leprae infection. Similar studies have been undertaken with the following groups of animals inoculated with M. leprae: (1) two rhesus monkeys, (2) 15 African green monkeys, and (3) three squirrel monkeys. To date one of the two rhesus and three African green monkeys (inoculated approximately six months before the other 12 African green monkeys) have developed lesions that were diagnosed histopathologically as lepromatous-type. In addition to the above, 12 rhesus were inoculated with titrated numbers of mangabey-derived M. leprae. Immune parameters were studied on multiple occasions prior to and after inoculation of these rhesus.

Lepromatous leprosy continues to be an important human disease, affecting approximately 12 million people throughout the world. The development of well characterized nonhuman primate models for experimental studies on leprosy is of extreme importance. The physiological similarities of these leprosy-susceptible species to those of humans will enable scientists to perform an extensive array of immunological studies. These immune activities will then be related to clinical, histopathological and bacteriological information on disease susceptibility and progression. The ultimate goal of this work is to develop an effective vaccine to prevent leprosy in humans.

- Intermediate Voltage Electron Microscopy for Cellular and Molecular Biology

A number of new methods for the investigation of cellular structure and function have been developed recently. Electron microscopy in particular has changed markedly as improved resolution and imaging techniques largely involving intermediate and high voltage instruments have evolved. Cell biologists have been using these methods to study cellular organization, structure and function at levels not previously possible.

Electron microscopy has recently been shown to be capable of biological structure analysis at resolutions between that of conventional morphological studies and the atomic detail of protein X-ray crystallographic studies. Components studied have included bacterial rhodopsin in purple membrane, helix destabilizing protein which is involved in DNA replication, cytochrome oxidase which is important in

cellular energy production, and gap junction complexes in cells. These studies require high resolution electron microscopes, preferably of intermediate or high voltage to improve resolution and the signal to noise ratio, with cold stages to minimize radiation damage and tilt capabilities to permit image reconstruction. In addition, the analysis involves significant image analysis and enhancement capabilities. Scientists are increasingly active in using the opportunities presented by such methods in studies of cell mobility, cell division and cytoplasmic structure in addition to studies of individual proteins or ordered components.

The Biotechnology Resources Program (BRP) has supported high voltage electron microscopy applications and methods development for cell biology for many years, and currently funds resource grants providing user access to the three one million volt electron microscopes in the U.S. devoted to biomedical research. The Program has also supported image analysis activities in biology and biophysics. Intermediate voltage electron microscopes (300kv-500kv) complement the very high voltage microscopes in structural studies of whole cells and in three dimensional morphology studies, and when suitably equipped can provide detailed structural information on proteins and other cellular components. As a logical extension of its high voltage electron microscopy support the BRP has issued a program announcement inviting grant applications for support of regional facilities for development and applications of intermediate voltage electron microscopy and image analysis.

- Human Chromosome-Specific Probes: Biological Materials Resources

Research on human genetic disease and on the genetic control of cell function will be greatly stimulated by the availability, shortly, of a library of human chromosome-specific probes.

The Department of Energy (DOE) has funded an effort to isolate and purify all of the human chromosomes in sufficient quantity to prepare and distribute chromosome-specific, uncharacterized cDNA probe libraries to 100-500 research laboratories. The flow cytometry facilities at both the Lawrence Livermore and Los Alamos National Laboratories plan to complete this joint project in 12-16 months.

The impact of this effort on the scientific community was discussed at two recent scientific conferences:

- Applications of Flow Cytometry to Gene Mapping and Chromosome Analysis, Santa Fe, NM. Oct. 23-26, 1983.
- The 34th Annual Meeting of the American Society of Human Genetics, Norfolk, VA. Oct. 30-Nov. 2, 1983.

The community believes that the application potential of the probes generated from the DOE effort across many areas of research in both human genetics and cytogenetics is enormous. Genetics researchers

see an immediate need to establish at least one centralized probe library and begin broad-based discussions on how best to facilitate the transfer and collection of the information which the use of these probes will generate.

Three separate elements of a human chromosome-specific probe repository were identified by scientists at both meetings:

- Chromosome Purification
- Probe Libraries (Generation, Amplification, Characterization, and Distribution)
- Archival Function (Data Collection, Correlation, and Dispersion)

The availability of this resource to the research community would enhance the rate of progress in many important areas of biomedical research. Obvious applications exist to mapping of the human genome. Such probes can provide diagnostic reagents useful in providing information in genetic counseling, and can aid in understanding the basis of inherited disorders. They represent an important opportunity for developing a technology that can improve public health and enhance medical care. Examination of the chromosomal abnormalities observed in neoplastic tissues may be aided through the use of these chromosome-specific probes.

This is a trans-NIH/trans-Agency issue and is but one example of a developing need for a Biological Materials Resources Program. A range of cell banks, tissue banks, organ centers, and cellular materials repositories have sought NIH support over the years. At this time no single program at NIH provides for coordination or support of such biological materials. The Division of Research Resources is in the process of examining the need for and requirements of a Biological Materials Program which would provide for coordination regarding support of resources such as a human chromosome-specific probe repository.

- Biomedical Research Support-Shared Instrumentation Grant Program

Through Biomedical Research Support Shared Instrumentation Grant (BRS-SIG) Program, DRR provides support for the acquisition of new, technologically advanced instrumentation in the \$100,000 to \$300,000 cost range to institutions with a high concentration of NIH-supported investigators whose research projects would benefit from the instrument on a shared-use basis.

In the past several years, evolving instrumentation technologies have provided capabilities that have become essential to permit optimal progress in a large number of NIH funded research projects in both basic and clinical laboratories. At present, many laboratories have only very limited access to such technologies which is not adequate for their present or future needs. Types of instruments which have

achieved wide use in the biomedical community and which are considered essential for certain areas of biomedical research include electron microscopes, mass spectrometers, nuclear magnetic resonance spectrometers, macromolecular sequencing equipment, x-ray diffractometers, image analysis facilities, computer graphic systems and cell sorters.

Two examples of a scientific area served by such instrumentation are given below: (1) A gas-phase microsequencer is being used by a group of seven investigators to augment their previously limited protein sequencing capability. The range of proteins, which can only be obtained in small amounts, includes carcinoma and melanoma-associated proteins; antigens from hematopoietic cells and rabies virus glycoprotein fragments. (2) A shared resource computer graphics display device is being used to deduce the bioactive conformation of the brain hormone corticotropin releasing factor. This peptide plays a key role in regulating endocrine, visceral and behavioral response to stress. Since the function of this peptide is determined by its three-dimensional structure, appreciating the conformational fluctuations that this peptide undergoes can lead to the future design of potential peptide drugs.

To date, in four years of operation, the BRS-SIG Program has received over 700 applications requesting over 150 million dollars in instrumentation. In FY 82, 83 and 84, 228 awards for a total of 37 million dollars were made to medical schools, graduate schools, research organizations and hospitals to try to meet the backlog of accumulated research instrumentation needs. The various type of instruments were placed in facilities that have commitment and skills necessary to use the equipment to its fullest capacities in both basic research and clinically applied research to ensure maximum utilization of the instruments.

- The PROPHET Network: Computer Network for Biomedical Research Support and Communication

The PROPHET Computer Network is the most comprehensive single set of tools currently available to the biomedical research community. It provides the biomedical research worker with an integrated set of interactive, graphic tools and capabilities for data storage, data management, data visualization, statistical analysis, curve fitting, mathematical modeling and simulation, as well as molecular modeling and amino acid and nucleotide sequence handling. The PROPHET computer connects to a national telecommunications system. Data may be entered, accessed, or analyzed from any location within the country. Scientific collaborations and shared research projects can be supported among investigators located at widely separated sites.

The PROPHET Computer Network provides research support, and communications links for biomedical scientists working in many specialties including cardiovascular studies, studies of drug design and efficacy, immunology and hematology and studies of the nervous, sensory and urinary systems. For example at the University of Pittsburgh,

Pittsburgh VA Medical Center, PROPHET has been used in a series of clinical studies in the area of infectious disease research. Extensive studies have been carried out relating to the clinical syndrome, environmental microbiology, and epidemiology of Legionnaires' disease. These studies have yielded new insights into the pathogenesis of this newly recognized disease. New methods of diagnosis have been evaluated and new approaches to prevention have been developed. PROPHET's technology permitted immediate testing of questions and hypotheses ("Is aspiration of contaminated water the mode of transmission?", "Are Legionnaires' disease patients different from patients with Pittsburgh Pneumonia Agent"?) without the need for retrospective chart review which is not only prohibitively time consuming but may be biased and selectively subjective. Generation of subsets, trend analysis, multi-variate statistical determinations, and graphic displays of data were performed in minutes using the PROPHET Network. In less than an hour, perhaps half a dozen specialists representing fields such as Epidemiology, Infectious Diseases, Microbiology and Radiology, sitting around a PROPHET graphics terminal, could collectively frame multiple questions and hypotheses and obtain instantaneous answers and insights into the origin, diagnosis, treatment and prevention of Legionnaires' disease.

The PROPHET Network presently supports over 900 scientific users at approximately 40 locations throughout the United States. Current computer technology makes it possible to deliver PROPHET's unique capabilities to a much wider scientific community, potentially encompassing all NIH-supported investigators in a national "NIH NET." The opportunity exists to enhance biomedical research productivity and creativity while linking scientists in a manner which will encourage them to share information and collaborate on joint research projects in a highly cost effective way.

The Biotechnology Resources Program has therefore initiated steps to update the PROPHET system. After an initial concept clearance, the program convened an advisory group to design the overall system and develop a specific RFP. During FY 1985 and FY 1986 it will be necessary to provide funding to both versions of PROPHET, in order to maintain service to current users while the new generation of PROPHET is being developed and phased in. A distributed computer network, encompassing user acquired intelligent terminals is recommended.

- Clinical Research Information and Data Management System (CLINFO II)

In 1970 the Division of Research Resources initiated an effort to determine the information processing activities and needs of clinical investigators, and to determine which of these needs could be met with the aid of computers. As an outgrowth of this effort, the Division has designed, built, tested, and distributed the CLINFO System to 23 General Clinical Research Centers. The CLINFO System is a minicomputer-based data management system, designed specifically to meet the needs of clinical investigators using the General Clinical

Research Centers. The CLINFO System has been well received by clinical investigators from a broad variety of disciplines, and has been purchased by several industrial organizations. At present there are more than 100 CLINFO terminals in operation. Additional systems are needed at a number of GCRCs. The future design of the system must also be planned (CLINFO II).

As an integral part of many General Clinical Research Centers (GCRCs), CLINFO is used daily for a wide variety of purposes. Some examples of research areas CLINFO has aided at the GCRCs are given below:

1. The relationship between blood glucose control and the late degenerative complications of diabetes has not been resolved. Recent advances in diabetes management, including use of portable insulin infusion pumps and self-blood-glucose monitoring techniques, have offered the potential to answer this critical question. A controlled randomized multi-center clinical trial with a large number of patients studied over long periods of time will be required. CLINFO was an integral part of a study designed to test the feasibility of such a multi-center clinical trial. Clinical centers in North America and England collaborated in developing a common protocol. CLINFO was used for collation and analysis of the 15,000 clinical and biochemical data points generated by the feasibility study.
2. In our congressional testimony last year, we discussed an automatic defibrillator which can be implanted without major chest surgery. CLINFO has formed the basis for analyzing the data from the 87 patients treated in this study to date.
3. CLINFO will be an integral part of a study of diagnosis and treatment modalities for immunodeficiency syndrome. CLINFO will be used to analyze retrospectively data from approximately 300 patients studied over the last 17 years. Data input will be histories, clinical data, laboratory data, and treatment regimens. CLINFO will allow retrieval of subsets of patients to obtain patient profiles at any time, in response to therapy (e.g., bone marrow transplantation) and to retrieve subsets of patients with differential diagnoses.

The success of the present CLINFO System has led to a substantial demand for additional systems. Currently, 23 GCRC sites with 26 separate centers and 244 (42%) of the 586 beds in the GCRC Program have access to CLINFO. Twenty-five Centers (20 applications) with 195 beds (33% of beds) have applied for CLINFO Systems and are pending review. It is anticipated that the remaining twenty-three Centers with 147 beds (25% of beds) will request CLINFO in FY 1985 or 1986.

As a result of its successful experience with the development of a computer system with wide applications in the clinical research environment, the Division believes that an intensified development

effort is warranted, with emphasis on exploring the feasibility of designing and testing of a nationwide clinical research information and data management system. To initiate this effort, a strategic planning group with expertise in clinical research, computer technology and information sciences, and clinical epidemiology and statistics has been assembled. This group has discussed the attributes and capabilities of current data management information systems for clinical research (CLINFO, PROPHET, and other systems). It has explored the potential for a new system designed to operate on microcomputers connected by a network and integrated with the present minicomputer hardware systems, and possibly connected to larger central computers. The requirements of the system are being specified and its parameters defined.

● Instrumentation Needs at Regional Primate Research Centers

The acquisition of various types of modern instrumentation items would greatly enhance the resources and research programs of the Regional Primate Research Centers.

Scientists in the seven Primate Centers conduct investigations in numerous biomedical areas. Many types of highly sophisticated instruments could be shared by investigators within the Centers, but are currently not available. Examples include transmission electron microscopes with greatly improved resolution capabilities for use in neurobiological, anatomical, pathological and reproductive biology research programs; automated quantitative microscopy systems for use in quantitative autoradiography studies to trace interconnections in the vertebrate nervous system and to map various regions in the vertebrate central nervous system; and various types of gamma/beta scintillation counters and ultrasound equipment for use in clinical medicine and reproductive biology studies. Other instrumentation, including diagnostic radiological equipment would greatly benefit the Centers' animal health programs and serve to protect their extremely valuable primate resources. Improved methods of information dissemination between the seven Regional Primate Research Centers are urgently needed and could be accomplished by an appropriate electronic linkage system. Electronic equipment, including closed television surveillance systems, are needed to provide appropriate security for the Centers' facilities.

Much of the existing research instrumentation in the research laboratories of the seven Regional Primate Research Centers is nearing obsolescence and must be replaced. Many types of modern instruments are not available at the Centers, but are urgently needed for important, state-of-the-art investigations in a number of biomedical areas. Communications and scientific collaborations among the seven Centers would benefit greatly from an electronic interlinking system. Acquisition of the PROPHET system, or an alternative system which can be adapted to interlink all Centers would promote the sharing of resources and scientific collaborations within the entire Program.

An electronic system of this type would also be helpful in the day-to-day ARP/DRR coordination and management of the overall Program. The need for adequate security, using modern electronic equipment, is increasing at the animal facilities of the seven Centers.

- Needs for Additional Diagnostic Laboratories

The Animal Resources Program supports 13 diagnostic laboratories located in major biomedical research settings across the country.

The laboratories provide for improved animal health programs through appropriate surveillance activities and investigation of naturally occurring disease and other laboratory animal problems, support studies resulting in new information on diseases of laboratory animals and their etiology, aid in the elucidation of new laboratory animal models of human disease, and develop resources including tissues, slides, photographs, etc., for research and training. These projects help undergird the NIH investment in animal related research projects at these and nearby institutions through their service related activities. The attached map shows the locations of the 13 diagnostic laboratories currently supported. It is apparent that additional laboratories are needed to provide diagnostic support to institutions not covered by current resources. In particular, major research settings in Florida, Pennsylvania, Texas, and California offer unique opportunities to establish new programs. Additional sites with potential include Oregon, Colorado, Louisiana, Wisconsin, Illinois, and Ohio. These new resources would help ensure the quality of animal related research in their geographical region while expanding research capabilities in laboratory animal diseases and animal model development.

The laboratories provide an excellent scientific opportunity in the area of pilot research and increasing the knowledge base of laboratory animal disease problems which can adversely affect research. For example, mycoplasmosis in rodents and encephalitozoonosis in rabbits are two common laboratory animal disease problems which frequently complicate research projects. Recent development of serological tests for these two diseases in the diagnostic resources will now allow screening of animals and contribute to elimination of infected animals prior to experimentation. Similar opportunities exist with such important problems as pasteurellosis in rabbits and a number of murine viral agents.

The focus on laboratory animal disease problems as complicating factors of research with an emphasis on diagnosis, pathogenesis, and control is unique to the Animal Resources Program. It is apparent that experiments with animals are becoming more sophisticated and of longer duration. Thus, there is an increasing need to ensure the health and well-being of animals used in research.

- Animal Facilities Improvement at Universities

This initiative would provide for a greatly expanded grant program involving alteration and renovation of existing, substandard animal facilities.

Animal facilities are an integral part of almost every research institution engaged in biomedical research. During the period 1956 to 1971, when the NIH received grant applications to support the construction of health research facilities, about 25 percent of the applications requested funds for construction of animal facilities. Projects to improve research animal facilities (alterations and renovations) have been supported by the Animal Resources Program. Over the past 13 years, 122 institutions have received improvement grants with awards totalling approximately \$16.8 million. These awards are limited to \$100,000 for alterations and renovations. This ceiling was raised from \$75,000 in 1982. It is apparent that this limited program is inadequate in meeting current needs in this area. Further, the Division of Research Resources has no authority for making grants for construction. Technological obsolescence has occurred in aging and deteriorating facilities which without new construction have been unable to institute advanced environmental support systems for animal care and utilization.

The most recent information pertaining to the magnitude of need in this area is the 1978 survey of animal facilities by the National Research Council, which revealed the following:

1. About 16 percent of all nonprofit biomedical research organizations reported a need for replacement of some animal facility space now in use, 38 percent reported a need for remodeling to protect the integrity of space now in use, and 43 percent reported a current need for additional space.
2. The 1978 needs of nonprofit biomedical research organizations for space replacement, remodeling, and additions to their animal facilities would have required \$350 million. Another \$407 million would have been needed to meet space needs projected from 1978 through 1988. These same organizations reported a need in their animal facilities of \$43 million for equipment renovation, replacement or additions.

Many of the nation's animal facilities constructed during the 1960s and earlier have deteriorated and become obsolete--many do not even meet the minimum requirements of federal animal welfare legislation. These facilities often need total replacement in order to provide advanced caging and watering devices, superior wall and floor coverings, systems for isolation of species, and innovations in a variety of environmental support technologies. These latter include important health support systems for temperature control and ventilation which are major facility improvements and most significant for proper care of laboratory animals.

In recent years, the Congress has focused increased attention on the adequacy of care afforded to laboratory animals. Legislation has been, and may again be, introduced which would require that all federally funded facilities be certified by a private entity as meeting particular standards with regard not only to animal treatment but also to physical environment. Even without specific legislative directives, NIH must take steps to assure that laboratory animals are adequately cared for. This initiative will enable the Division of Research Resources to support replacement and major renovation of necessary facilities.

- Needs for Repairs and Renovations of Facilities and Major Equipment at Regional Primate Research Centers

The research and animal facilities, as well as major fixed and moveable equipment items at the seven Regional Primate Research Centers have received intense usage for over 20 years. Many of these facilities and equipment items are currently in urgent need of renovation, repairs or replacement. This problem is a subset of the needs for animal facility renovation at universities described in the previous scientific opportunity document.

The seven Regional Primate Research Centers were constructed during the period of 1961 to 1965 with federal (NIH) funds on a nonmatching basis. Heavy and prolonged use of these physical plant facilities and fixed, moveable equipment items over the past 20-24 years has resulted in their marked deterioration. Significant needs are apparent at all seven Centers for repairs and renovations of buildings and research laboratories, including the continued maintenance and upgrading of their primate animal facilities and related animal care equipment. These deficiencies must be corrected to maintain high quality, efficient resources and research environments which are used by over 650 biomedical investigators annually.

The seven Regional Primate Research Centers were established by NIH to serve as regional and national research resources of long-term nature. The research programs carried out in the Centers are closely related to the categorical interests of NIH. The federal government has a major investment in these Centers, and the physical facilities and equipment items critical to their effective operations in the future must be properly maintained. The significant costs associated with these needs cannot be adequately met from the operational budgets of the Centers. A recent, detailed engineering assessment indicates that the total costs for facility repairs, renovations and replacement of major fixed equipment at the seven Centers during the next five years (1984-1988) will be approximately \$13 million. Congress added \$1,000,000 in the FY 1984 budget as a start toward meeting some of the highest priority needs of this nature.

- Increased Opportunities for Minorities in Research
Undergraduate Colleges

Large numbers of minority students enroll in small four-year minority colleges. With the shift in MBRS program emphasis from institutional support (1971-76) to individual faculty research sub-project support, it has become more difficult for these institutions to compete successfully for MBRS funds.

A new approach, developmental in nature, is needed which would provide basic institutional support for initiation and support of biomedical research activities in these smaller schools.

This area was identified as a high priority need by the Council MBRS Work Group Retreat participants and subsequently endorsed by the GRSRC and program directors at their annual meeting on March 8-10, 1984.

Small undergraduate institutions have had limited success in competing for MBRS support. The use of new mechanisms is necessary in order to have a more meaningful involvement of these institutions in increasing the number of minorities with the expertise for pursuing biomedical research careers. These institutions have played and continue to play a major role in educating a substantial proportion of minority students. A recent report by the Educational Testing Service indicates that Black colleges award 40 percent of the baccalaureate degrees which Black students receive, even though these colleges enroll only about 17 percent of the Black college students enrolled throughout the country. However, budgetary constraints and mandated educational missions prevent the use of institutional funds to support and develop the infrastructure which is needed for conducting scientific research at these colleges. Faculty teaching loads are prohibitively high (16-20 contact hours/week). This tends to have, even with allowable MBRS release time, an adverse effect on faculty research productivity as measured by scientific publications and acquisition of competitive research grants. Therefore, traditional research support mechanisms have not addressed the problems of initiating and maintaining research programs at these schools.

The principal objective is to develop an environment which will provide increased opportunities for minority undergraduate students to pursue advanced degrees in biomedical research and provide the faculty an opportunity to engage in biomedical research.

The scope will involve support for pilot studies to allow faculty to initiate research in their respective disciplines; support of scientifically meritorious research appropriate for an undergraduate college environment; support for the participation of students in meaningful biomedical research experiences; support for seminars and

workshops in order to provide students with additional research exposure and role models; and support for faculty and student attendance at scientific meetings in order to present scientific papers on their research, familiarize themselves with recent advances in science and become familiar with research career opportunities.

- Increased Opportunities for Minorities in Research
Thematic Project Grant

The Division of Research Resources made its first awards through the MBRS Program on June 1, 1972. During the ensuing years there have been some marked changes at some of the MBRS-supported institutions.

One of the most significant changes which has occurred is in the increased biomedical research competence of the faculty. This has come about in part, as a result of MBRS support which has allowed some institutions to recruit and retain biomedical research-oriented faculty.

A logical consequence of this expanded faculty research competence has been the development of new research areas around which faculty with similar research interest are now clustered (e.g., biochemistry, molecular biology, immunology, biophysics, environmental health, molecular genetics, behavioral science or toxicology).

The current MBRS mechanism does not allow for more than one application from each institution. A new mechanism is needed which will allow these institutions to submit multiple applications, each addressing a more focused area of research.

The current emphasis of the program is on individual faculty research projects and an institution can submit only one application. If a department or a group of investigators wants to submit a proposal for developing a new area of research such as gene cloning or hypertension, they must submit it at the time that the institution submits an MBRS application along with a multitude of other individual research projects. The resulting MBRS application is extremely large and difficult to review. The timing for submission from a department or a research group may not coincide with the rest of the institution's deadlines. As a consequence, some investigators with good research ideas are not afforded the opportunity to contribute to the institutional research environment. The thematic approach will provide for developing their biomedical research capabilities on a more timely basis by allowing them to submit multiple MBRS applications emphasizing different themes or departmental thrusts, and encourage increased communication between co-funding Institutes and groups of MBRS investigators. In the pilot phase, eligibility will be restricted to institutions having 50% or more minority student enrollment.

- Increased Opportunities for Minorities in Research
Faculty Career Enrichment

Relatively few faculty at MBRS-eligible institutions have been successful in competing for non-targeted research support; a large number of faculty, at the undergraduate colleges especially, have had a low success ratio when competing for support in the MBRS renewal application. Thus, there is a need to develop a mechanism which will update and expand the faculty research capabilities at these smaller institutions.

Expanded research career development of faculty at MBRS-eligible institutions is proposed by instituting Research Career Enrichment Awards which would provide off-campus research experiences at research intensive laboratories for periods of up to one year and for them to initiate research and develop competitive research projects for future MBRS or other research support with consequent opportunities for continuing collaboration with scientists at host laboratories. These awards would be available only to faculty who are holders of the terminal degree at undergraduate institutions with 50% or more minority student enrollment or with a substantial minority student enrollment and a history of commitment to training minorities as determined by the Secretary, DHHS. Health professional schools and other institutions that offer the doctorate degree are not eligible.

Faculty members in many MBRS institutions are not making the transition from teaching as a primary function to part-time engagement in competitive biomedical research. Many begin their MBRS research as an extension of the doctoral dissertation or research projects initiated at some point earlier in their career. However, since new advances are occurring rapidly in all areas, such research projects may be scientifically meritorious but not at the leading edge of scientific endeavor. Continuing institutional commitments (teaching, student advisement, committee assignments, etc.) may not have allowed time for the effort necessary to update research skills and knowledge. Other limiting factors include lack of adequate library resources focused on research and relative isolation of some MBRS institutions from centers of biomedical research activity. In order to become competitive, some MBRS institutions, especially the undergraduate schools, need ways to upgrade not only facilities and equipment but also faculty skills and knowledge.

The proposed award would consist of salary support (not to exceed the maximum level allowed for Research Career Development Awards) travel allowance and supplies and/or other modest support to carry out the research at the host institution. Once these faculty return to their home institutions, some research support will be necessary to continue the studies initiated at the host laboratory; these studies could serve as the basis for developing a competitive research application, principally but not exclusively, for the MBRS Program. A continuing collaborative arrangement with the host research institution would be expected to exist.

This initiative could be implemented as a K series award, not subject to NRSA ceilings. This program would focus on short-term (semester or summer) research experiences and thus would complement the current MARC program which offers training under NRSA for longer periods of time (one to three years).

- Increased Opportunities for Minorities in Research
Two-Year Colleges

Two-year community colleges represent the most accessible type of higher education for American Indians, as well as for a large percentage of Hispanics (particularly in Texas and California) and for large numbers of Blacks. Approximately 50% of minority college students are in two-year colleges.

A new program is needed which would provide the experiences and exposure to biomedical research as a career option for these students.

The current emphasis of the MBRS Program on individual faculty research projects does not effectively address the needs of community colleges or provide the research experiences and exposure needed by minority students enrolled in two-year institutions. Only a handful of these schools have successfully competed for MBRS funds, leaving this vast minority student pool largely untapped. In addition, very few community colleges have applied, suggesting that current program guidelines are not suitable for this type of institution, whose primary purpose is not research-oriented.

A program is being developed which will focus on selecting those students who have potential for and/or interest in continuing their education beyond the two year institution and motivating those students toward careers in health-related fields. Examples of program elements are: (1) establishment of seminar series featuring visiting minority role model scientists, (2) development of co-op options and/or summer apprenticeships in biomedical research laboratory settings, and (3) participation in research seminars and workshops at nearby institutions. The use of these approaches and others providing exposure to biomedical research at research-oriented institutions should be much more effective than the current program in terms of making minority students at these institutions aware of career opportunities in biomedical research.

- Animal Resources Program--Investigators in Laboratory Animal Science

Summer fellowships, institutional postdoctoral programs, individual post doctoral fellowships, and a special research career award (K01 program) are supported by the Animal Resources Program (ARP).

Well-trained investigators with a background in laboratory animal medicine are key to carrying out the Program's research and resource objectives. Such individuals will be needed in the future to establish new diagnostic resources, lead the search for additional animal

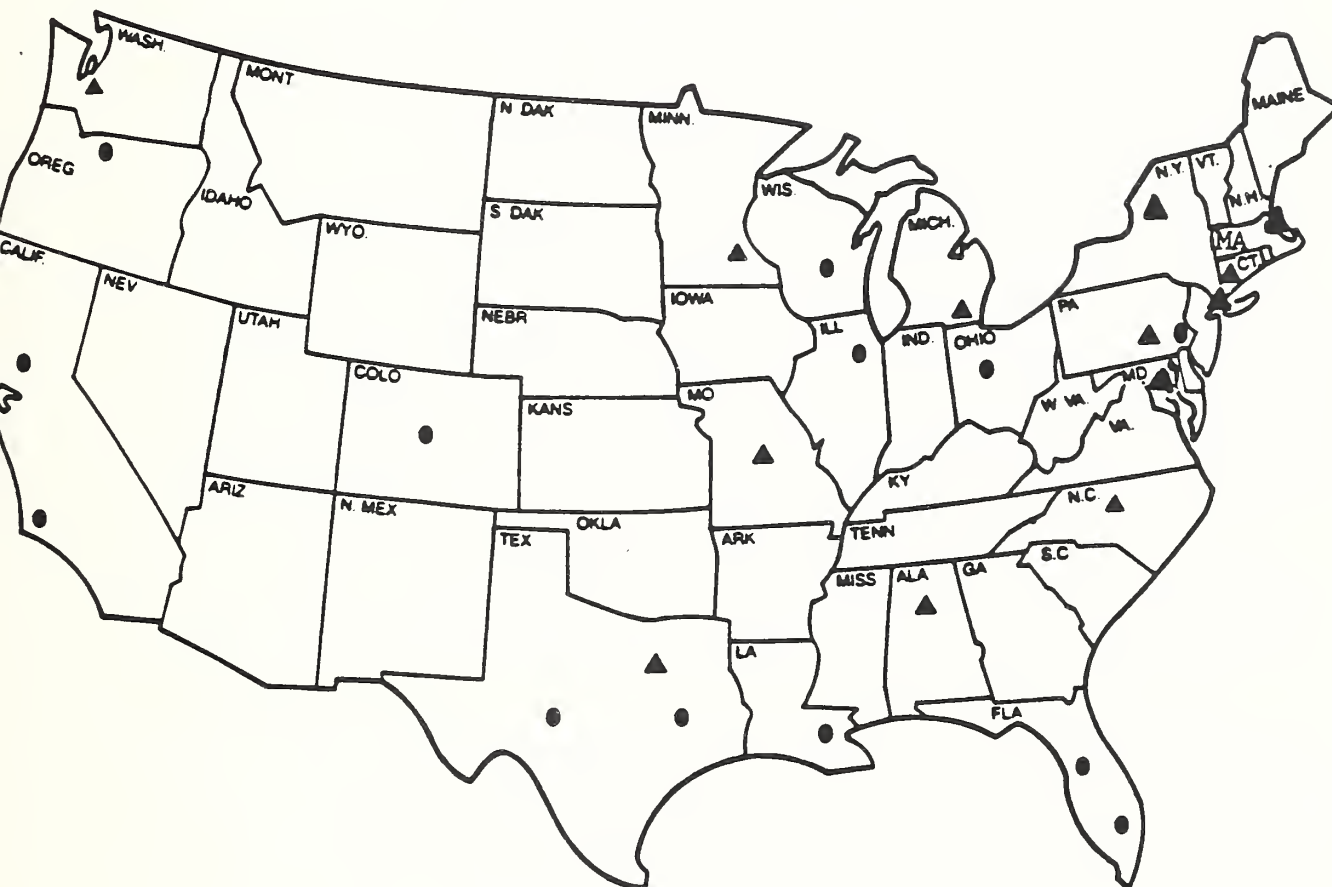
models, and help solve problems of intercurrent disease in laboratory animal colonies.

An important element of manpower development involves reaching potential candidates for postdoctoral training during the formative stages of their professional education. For the past eight years, training programs and diagnostic laboratories supported by the Program have been encouraged to employ veterinary students during their summer break. From 10 to 15 institutional programs involving 20-30 students have participated each year. Critiques of the students involved are submitted to ARP and, in turn, are distributed to all the institutional participants. It is apparent that this work experience is resulting in greater knowledge and interest in the field of laboratory animal medicine. It appears that approximately half of the postdoctoral appointments to ARP regular institutional training programs are coming from this "pool" of former summer students. This approach offers several advantages over the Short-Term Training Program (T35) in that students from any veterinary school may participate, they are introduced to biomedical research in a medical school setting, and their research experience is more likely to involve a comparative medicine problem.

There are nine currently active training programs with a total of 31 funded positions. In addition to these institutional awards, two individual postdoctoral fellowships are currently active. Since the average training period is two and one-half years, there are usually 8-10 graduates per year. Currently available figures indicate that 189 trainees and fellows have completed training since the inception of the training grants and fellowships in laboratory animal science and medicine. Sixty-six (66) of these are employed by medical schools and 75 by other academic, research or governmental organizations. The majority (112) are serving as directors or staff members of a vivarium; 62 are engaged in teaching and research or are obtaining additional training; and 15 are in public health, private practice or are retired. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

Additionally, the Program has initiated a Special Emphasis Research Career Award (SERCA) in Laboratory Animal Science. This award emphasizes in-depth experience for the laboratory animal specialist in various fundamental and clinical scientific disciplines. This special award is made to develop multidisciplinary veterinary researchers who will direct their research toward refining the use of laboratory animals in biomedical research, the study of significant laboratory animal disease problems occurring in vivarial settings, and the development of new animal models useful in solving biomedical research problems. The first applications for this award were received in FY 1983 and four new awards were made. It is expected that this will remain a limited and highly selective program with one to two new awards each year.

Geographic Locations of Animal Diagnostic Laboratories (13)



▲ Animal Diagnostic Laboratories

● Proposed Sites

JOHN E. FOGARTY INTERNATIONAL CENTER FOR
ADVANCED STUDY IN THE HEALTH SCIENCES

I. Program Overview, FY 1986

The Fogarty International Center (FIC) is the focal point for NIH programs and activities that involve foreign scientific institutions or organizations, and that foster cooperation between United States and foreign biomedical and behavioral scientists and researchers. These international activities of the NIH contribute to the advancement of biomedical knowledge, disease prevention and health maintenance in the United States as well as abroad. The Director of the FIC also serves as the NIH Associate Director for International Research. In these dual roles, the Fogarty International Center has an important impact on the national health scene: experience and talent from abroad as well as scientific opportunities and technologies developed and tested elsewhere in the world can be brought to the United States. The FIC also helps to insure that research funds are used effectively when United States and foreign scientists bring complementary skills and approaches to bear on common problems, and when scientific resources available elsewhere are not duplicated. These activities contribute to the ability of the United States to maintain its leadership position worldwide with regard to research and development in the biomedical sciences.

The Fogarty International Center now fulfills its mission through four major programs: Advanced Studies; International Research and Awards; International Coordination and Liaison; and Foreign Scientists Assistance.

In 1982, the FIC was designated as the WHO Collaborating Center for Research and Training in Biomedicine. This designation, for a four-year period, provides an exceptional opportunity for the U.S. (NIH) to expand its leadership role in international biomedical science, to expand and support the network of relationships with counterpart research institutions of other countries, and to undertake other special initiatives in research training, technology transfer, information dissemination and other activities in support of international biomedical research collaboration.

FIC also is the organization through which funds are appropriated annually by the Congress to the Gorgas Memorial Institute for core support for operation and maintenance of the Gorgas Memorial Laboratory (GML) in Panama.

II. Areas of Opportunity

● Advanced Studies

Since its inception, the Fogarty International Center has fostered advanced studies on international aspects of biomedical research.

During FY 1983, the Advanced Studies area was reorganized to provide additional emphasis to the study of international issues. It is now composed of the International Studies Program, the Scholars-in-Residence Program, and a component which manages conferences for the Center.

The International Studies Program is designed to identify health research issues of international concern and to develop feasible strategies for addressing these issues. This program both draws upon and complements the other components of the Advanced Studies Program, and obtains advice from both within and outside the NIH.

As part of this program, the Fogarty International Center (FIC) began an effort to focus world attention on the potential for eradication of selected infectious diseases in May of 1980. A workshop was held at the NIH and a number of infectious disease candidates were evaluated for improved control and potential eradication. International symposia have been held on the following diseases: measles in the spring of 1982, paralytic poliomyelitis in the spring of 1983, congenital rubella infection in March of 1984, and yaws and other endemic treponematoses in April of 1984.

The spring '82 measles conference has had an important impact internationally. Several nations, including the Soviet Union, Sweden and Finland, have made the elimination of measles a national health priority. A still larger number of countries, both at the governmental and practitioner levels, have recognized the importance of expanding their immunization programs and have within the past year mounted intensive campaigns, (e.g. in France). The United Kingdom has also attempted to improve the percentage of population immunized.

The international symposium on control of paralytic poliomyelitis was held in the spring of 1983. Participants concluded that eradication is not feasible in this century, but remains a distant goal. Polio is not the number one health priority in nations with very serious health problems where limited resources are being used to address diseases having higher mortality and morbidity rates. Nevertheless, an important result of the polio conference was to demonstrate that paralytic polio is more of a problem than most nations realized, particularly in the developing world. Although paralytic polio has been essentially eliminated in the United States, 65 percent of the world's nations are still burdened with this disease.

An international symposium on the prevention of congenital rubella infection (and subsequent rubella birth defects) was held in Washington, D.C., in the spring of 1984. Vaccine strategy is very important. The United States chose universal vaccination of children and broke the chain of epidemics. The number of rubella-related birth defects has dropped steadily since the last epidemic in 1964-65 when there were 20,000 cases. In 1983 there were only seven cases. Selected vaccination of pre-adolescent girls and young women has not worked in most countries which utilize a selective vaccine strategy. The rubella vaccine was demonstrated to be safe, even for inadvertently vaccinated pregnant women, and the immunity that it elicits to

be long-lasting. Rubella vaccination programs are expected to prevent 10,000 cases of deafness by the end of this century, with estimated savings in health care and education costs of over two billion dollars.

The meeting on yaws and other endemic treponematoses resulted in a significant international call for action. WHO had called world attention to this problem in a resolution of the 31st World Health Assembly of May 1978 entitled, "The Control of Endemic Treponematoses" which emphasized the urgent need for prompt and vigorous action in the control of the treponemal diseases which mainly afflict children often in the poorest and most remote areas. Nevertheless, because of inadequate surveillance and follow-up control efforts, yaws now afflicts more than one and one-half million individuals worldwide, and is on the rise, particularly in West Africa.

Penicillin is still as effective against yaws as it was 30 years ago. However, at the Fogarty Center meeting it was noted that, although resistance by the bacterial spirochete has not yet arisen to penicillin, clinical experience with antibiotics has shown that resistance can develop quickly even after decades of high sensitivity. Thus, it behooves the global community to renew efforts to interrupt the human transmission of yaws and other endemic treponematoses and bring them under complete control while there is still a simple, inexpensive, and highly effective cure.

The FIC anticipates a systematic re-examination of both research needs and progress toward eradication of these diseases beginning in FY 1985-1986, and will also initiate a long-term assessment of biotechnologies from an international perspective.

To complement FIC's participation in the international conference grant program, extramural resources will be drawn upon by the Advanced Studies Program by initiating a Small Grants Program for the Assessment of International Issues in Biomedical Research.

Another component of the Advanced Studies Program is the Scholars-in-Residence Program. FIC Scholars-in-Residence are distinguished United States or foreign scientists who spend up to 10 months at the NIH to share their knowledge, skills, and ideas with each other and with NIH scientists. They conduct research in collaboration with NIH intramural staff and contribute to the intellectual environment on the campus through seminars, informal exchanges and conferences. To maintain collegial activities, including joint seminars, a basic number of scholars need to be in residence to ensure opportunities for intellectual interaction. Approximately ten Fogarty scholars will be given awards.

The scientific opportunity which exists is the full implementation of FIC's mandate to conduct advanced international studies. The NIH Director's Task Force Report of 1979 recommended the development of an advanced studies program. With the designation of a branch chief and senior staff in FY 1983, and the initiation of selected studies

in FY 1984 and in FY 1985, the program should begin to have significant impact in FY 1986. The focus will be on issues concerning the international aspects of biomedical and behavioral research, research manpower training, and the transfer of research results to the health care system. Areas of study will be selected from the following topics: international issues in technology assessment with an emphasis on biotechnologies; the assessment of the United States position with regard to research and development in biomedical sciences; and the feasibility of control or eradication of particular diseases, especially infectious diseases, which have high prevalence worldwide with implications for the United States. Other types of issues proposed are: NIH's role and responsibility in addressing health problems in developing countries; issues in the appropriate conduct of science as applied to international research activities; and NIH's role in international disease prevention; and the nature of biomedical research collaboration in developing countries.

It is particularly important to build this program (which was re-organized in FY 1983 and which now has discrete program identity) so that the FIC can have a viable facility for the evaluation of various issues of international relevance in biomedical research and for the examination of factors necessary to maintain U.S. leadership in the biomedical sciences.

- International Research and Awards

Under the International Research and Awards Program, United States and foreign scientists are offered opportunities to study abroad and in the United States, respectively. Fellows and their sponsors pursue a broad range of biomedical research programs that are of mutual interest.

International Research Fellowships: Since the International Research Fellowship Program began in 1958, over 2,500 fellowship awards have been made to foreign scientists to extend their research experience in the United States. In most cases, the exposure to new ideas and approaches has had a stimulating effect on the fellow's future research career. Participation is through one of 50 established nominating committees. To increase the number of scientists in the program in FY 1986, we plan to work with umbrella scientific organizations and other groups in addition to the nominating committees.

Senior International Fellowships: These fellowships offer opportunities to established United States scientists to pursue collaborative research abroad, enable them to contribute to the research advances of the host laboratory as well as acquire new information and new skills to enhance their own research experience and teaching ability. Over the past several years, the SIF Program has been reduced significantly at a time when funds from private foundations have been eliminated. Therefore, it is important to increase the number of SIF awards to a level that will make it attractive for scientists to apply. Over three-fourths of the SIF recipients have taken fellowships in institutions in Western Europe, particularly the United Kingdom. To encourage a wider geographical distribution of fellows

and to follow-up on International Issues Studies, such as polio, measles, schistosomiasis, and yaws, special SIF awards will be made in which a team of scientists will conduct collaborative research in countries where these conditions are still major health problems.

The scientific opportunities for the United States via the International Research and Awards Programs are varied. These fellowships provide foreign and United States scientists with the opportunity to obtain the latest skills and contribute to the latest advances in the biomedical and behavioral sciences. Many present scientific leaders in advanced as well as developing countries have had their initial scientific experiences in collaboration with United States scientists. This program also facilitates contacts with specific countries for future studies.

In the IRF Program, it is necessary to maintain active participation by the 50 cooperating countries and the respective scientific communities. It is also important to establish contacts with new countries and the developing countries of Africa. Full participation of the 50 nominating committees will result in an average of only two awards per country. Further, the research projects conducted by the International Research Fellows typically require more than one year to complete. The SIF Program has been functioning at a minimal level of about 30 awards per year. It is important to provide additional opportunities for senior United States investigators to conduct collaborative research with scientists from other countries. In addition to pursuing additional traditional relationships among scientists of industrialized countries, the FIC is considering the expansion of the concept of the SIF award so that it would include the provision of a multiple award (from 3 to 4 scientists in sequence or as a team from the United States to work with scientists in a single host institution).

- International Coordination and Liaison

The International Coordination and Liaison Program of the Fogarty International Center serves as an operational and coordinating link between foreign countries and NIH Institutes and Divisions, other U.S. agencies, and international organizations concerned with problems of world health. Because numerous NIH Institutes (in some instances as many as 9 or 10) participate in bilateral agreements with a given country, the liaison provided by the Fogarty International Center helps to ensure smooth coordination of complex relationships. At present there are 50 bilateral agreements with 29 countries, the most recent additions being Finland in 1982, China in 1983, and Belgium in 1984. During FY 1983, the FIC assumed the lead PHS coordinating role for bilateral agreements with nine countries (Belgium, France, Germany, Hungary, Japan, Poland, Romania, Venezuela, and Yugoslavia).

The Center also supports individual exchanges of well-qualified United States and foreign health scientists who wish to collaborate in research. The scientists are jointly supported through agreements the United States has with five Eastern European countries and France. Additional Individual Health Scientist Exchange Programs are being initiated or are under development with China, the German Democratic Republic, Bulgaria, and Israel.

The liaison and support activities provided by the FIC with other components of the NIH, United States agencies and international organizations ensure the smooth coordination of collaborative research and training endeavors. Bilateral agreements in the areas of science and technology as well as health have been of immeasurable value in reducing social and political barriers to scientific exchanges. These collaborative activities capitalize on unique features of local environments and resources and foster the use of shared technical and professional resources and the cost of these exchanges.

In recent years there has been a review of many of the existing agreements between the United States and other governments by various elements of the Executive Branch. In addition there have been new administration bilateral science and technology initiatives in which NIH has been requested to participate but for which support monies have not been provided. NIH research Institutes do not have a line item in their budgets to support international biomedical research. With recent Administration foreign policy initiatives in India, ASEAN countries, Egypt, and Japan, constraints are already forecast which will adversely affect our future capacity to support international initiatives. In addition, other opportunities often arise for NIH to promote intergovernmental collaboration for the purpose of advancing United States medical knowledge but are passed up because of budget constraints and other priorities.

- Foreign Scientists Assistance

Under the Foreign Scientists Assistance Program (FSAP), the FIC provides coordination and administrative services for the NIH Visiting Program and the NIH Foreign Guest Researcher Program. Both of these programs enable experienced foreign scientists to work at NIH with senior NIH investigators on problems of mutual interest. In FY 1983, these programs provided services to 1,238 Visiting Program participants from 62 countries, and 442 Guest Researchers from 64 countries (an overall increase of 13 percent from FY 1982). The FSAP also provides visa and other support services for foreign experts, for special exchange scientists, for the dependents of participants, and for foreign patients in the Clinical Center.

The opportunity which exists is the ability of the FIC to continue to be responsive to the program needs of the intramural programs of the NIH. The Visiting Program participants constitute approximately one-third of NIH's professional intramural staff and, thus, are a very valuable scientific resource.

The NIH Visiting Program and the NIH Foreign Guest Researcher Program are priorities of the NIH Institutes, who bring outstanding scientists to the United States to conduct research or receive advanced research experience in the NIH intramural laboratories. The number of participants in these programs increases each year. Some of these participants are staying longer at the NIH than in prior years, which increases the complexity of the work required to satisfy immigration regulations to extend their stay in the United States as well as to meet income tax requirements. Expansion of program support to additional PHS agencies is expected as these agencies experience constricted staffing problems and look to FSAP/FIC to provide the expertise to assist them. These concerns necessitate an increased staff size which has the capacity for working with NIH Scientific Directors, their staffs, foreign scientists and with high-level scientific and administrative staffs of other PHS agencies.

Stabilization of the Visiting Program is being considered. The current active, or "on board," levels at any time are approximately 340 Visiting Associates and Scientists, and 575 Visiting Fellows.

- FIC-WHO Collaborating Center for Research and Training in Biomedicine

FIC was designated as the WHO Collaborating Center for Research and Training in Biomedicine for a period of four years beginning June 1982. This WHO Collaborating Center responsibility relates to the WHO Office for Research Promotion and Development in Geneva and to comparable offices in WHO Regions. In FY 1983 a staff person was recruited with appropriate background and contacts to develop this program.

Illustrative activities to be initiated in FY 1986 include: (1) WHO-FIC international workshop on the role of NIH in strengthening research and research training in developing countries; (2) WHO-FIC regional seminars as follow-up to FIC's recent international conference series on global eradication of infectious diseases (to identify research needs and the application of research findings to improve control); (3) WHO-FIC international workshop on the potential applicability of institution-building methods of the United Nations Development Program/World Bank/WHO Special Programme for Research and Training in Tropical Diseases to other communicable and chronic diseases.

As the focal point for NIH international research activities, FIC has a leadership responsibility to facilitate new and strengthened ties in biomedical and behavioral research between leading United States scientists and institutions and their counterparts in the developed and developing world. A plan of action has been developed which applies FIC programs in research and training and integrates interests of other NIH components, as appropriate, in the Collaborating Center's primary mission of strengthening institutional research and management capabilities for prevention and control of major diseases throughout the world.

NATIONAL LIBRARY OF MEDICINE

I. Major Program Changes, FY 1986

In FY 1986, NLM will expand its Computers in Medicine (Medical Informatics) Research and Research Career Development program and extend it through a new initiative to develop Centers of Excellence in Medical Informatics. The purpose is to provide stable, long-term support for multi-project, multi-disciplinary approaches to the application of artificial intelligence techniques to expert systems in medicine. The Centers will develop in concert with a strengthening of the Lister Hill National Center for Biomedical Communications' intramural research programs in complementary areas. The Integrated Academic Information Management Systems (IAIMS) initiative, which began in FY 84 with strategic planning projects for prototype development, will expand into a second phase. Pilot demonstration projects to test the feasibility of medical center-wide IAIMS prototypes will be accorded high priority.

II. Areas of Opportunity

- Computers in Medicine (Medical Informatics) Research and Research Career Development

Since 1973 the NLM has been the sole NIH grants source for training associated with computer applications in medicine. In 1979 the Library also initiated a complementary effort for support of research projects, program project and research career development in this field. This comprehensive medical informatics training and research assistance has stabilized in recent years (with decreasing dollars available for new awards) to represent approximately 45-55% of NLM's annual grant appropriations for fiscal years 1983, 1984 and 1985 (projected). In addition to these on-going priority activities, NLM will plan, in 1986, to initiate an adjunct effort in its support of Medical Informatics. A program for the development of "Centers of Excellence" in this field is described elsewhere. In 1986, resources will provide start-up funds for the "Centers" initiative, the continuation of a selective program of investigator initiated research in medical informatics and the maintenance support for the five institutional training awards first made in FY 1984.

NLM shares with all other NIH BID's a vested interest in the development of a new generation of health information transfer methods. Accordingly, in our continued and expanded efforts in the Medical Informatics arena, the Library will remain mindful of multidisciplinary features of this total arena and therefore seek the collaboration of other Federal funding entities where this is feasible and appropriate.

A recent NSF study reached two significant conclusions regarding computing in higher education: "There is a major crisis in training computer scientists," and "other nations have recognized the role of computing in the development of their national plans and are investing in research and training with a focus and on a scale not found in the U.S." The conclusions apply with special force to the health sciences. As a minimum, the decade of NLM support for training and the solid body of experience gained through research support has given visibility and credibility for this evolving multidisciplinary field. The opportunity is extant on two fronts to exploit the progress made and to assure that the advances are not attenuated:

1. to provide the developing community of research scientists in medical informatics with meaningful, sustained levels of support and research challenges in a variety of categorical health areas, and
2. to continue to attract and develop creative young research scientists who will advance information synthesis and knowledge access and become the leaders in establishing or strengthening academic departments in medical informatics.

American medicine has been a leader in using and developing new technologies to advance the understanding of life processes. Nowhere is this more apparent than in the utilization of computers in the health sciences; the progress has been truly remarkable and is widely publicized. As experience with computer technology in research and patient care has grown, attention has shifted from using the computer as a tool to exploring it as an adjunct to human cognition. Although research into the organization, synthesis, and utilization of information by computers is just beginning, it is clear that the potential for artificial intelligence systems in medicine is great indeed.

Research and development for the health computer sciences must be expanded, but there is concurrent need to train highly competent investigators for these activities. In medicine, as has been found in the other sciences, the small number of creative scientists available for computer technology and artificial intelligence research represents a major crisis. Important objectives will be to provide increased training opportunities in the health computer sciences and to continue to foster research investigations to include:

- Techniques for convenient bibliographic retrieval from large computerized databases, thereby permitting physicians and nurses to search the literature without a specially trained intermediary.
- Refinement of peer revalidation of the scientific accuracy of the biomedical literature leading to higher standards of medical writing and editing.

- Better understanding of information structure as revealed by linguistic analysis of medical records and reports, thereby enabling improvement in the organization of medical knowledge.
 - New ways of adapting knowledge to computerized clinical problem-solving and decision aids. This work includes better understanding of the role of knowledge in medical judgment.
 - Growth in the number of computerized expert knowledge systems for selected medical problems. These systems using artificial intelligence methodologies draw inferences, compute probabilities, and explain their own reasoning process.
- Centers of Excellence in Medical Informatics

In FY 86 NLM will initiate a new program for Centers of Excellence in Medical Informatics. Over five years, approximately 12 Centers will be developed. The Centers will receive support for comprehensive programs that encompass research training and career development, curriculum enhancement, and advanced research investigations. The purpose of the Center is to demonstrate the practical utility of medical informatics in carrying out the fundamental purposes of the institution, through research and applications in the classroom, the clinical laboratories, and the bedside.

A landmark 1963 report of the President's Science Advisory Committee observed that "Transfer of information is an inseparable part of research and development and [all those involved] must accept responsibility for the transfer...in the same degree and spirit that they accept the responsibility for research and development itself." Over the intervening 20 years, medical informatics has become the leading discipline in responding to that challenge. The NLM has been the principal Federal agency to fund investigators in medical informatics. Even though funding has been sub-optimal, NLM's grantees have become acknowledged national experts in this arena. The Center program builds upon this foundation.

Having nurtured the expertise, the time has come for NLM to intensively cultivate an environment in which medical informatics can attain maturity as a discipline and have optimal impact on medical students, young physicians and other health care providers. To succeed, Centers need stable, long-term support for multi-project, multi-disciplinary approaches. A secure environment is essential for fostering young investigators and probing the profoundly complex problems in medical intelligence systems.

There is an immediate and critical need to consolidate the ground covered in medical informatics development over the past two decades and to provide the basis for strong forward progress through robust and vigorous Centers of Excellence in Medical Informatics. It is widely accepted that this country must meet the challenge of fifth generation computer development in other countries. NLM's program, while only a small fraction of that effort, is an important one.

- Integrated Academic Information Management Systems (IAIMS) Prototype Development

Recent reports issued by the Association of Academic Health Centers and the Association of American Medical Colleges call for the abandonment of incremental planning and a reformulation of current approaches to the leadership and administration of information resources in academic medical centers.* Currently health information systems are non-standard and proliferating in an uncoordinated fashion.

In FY 1984 the NLM recognized the problem area and initiated a program for the planning, testing, and development of medical center-wide integrated information network prototypes. In September 1983, competitive contracts for strategic planning were awarded to the Georgetown University, Columbia University, University of Maryland, and University of Utah's medical centers. Several grants supporting similar planning efforts will also be awarded in FY 1984. The purpose of the IAIMS program is to a) promote strategic planning for institution-wide linkages between the library related systems and data bases and the emerging clinical practice and health sciences learning data bases; b) improve cost effectiveness of institutional resources management; and, c) support the use of present day technologies to more effectively diffuse and transfer new scientific findings to assist health professionals.

There can be no doubt that sophisticated technical information data bases can lead to greater economies in and higher quality of health care, education and research. A number of universities are in the process of creating institution-wide information network systems. This is the time to assist medical centers to make a swift and systematic change-over from manual and human memory-based systems to sophisticated health knowledge systems. The NLM is the only agency providing leadership in and training, research and resource project programs for biomedical communications. It is, therefore, uniquely positioned to enhance and accelerate research in and applications of new technologies in this critical area.

The information system that supports all advances in society consists of the generation of knowledge through research, its validation through publication and application, its storage for wide-spread future uses, and its retrieval to enable the generation of new knowledge. This entire information system, worldwide, is converting to digital data bases for ease, rapidity and economy of use. It is

* Piemme, T.E. and M.J. Ball, Executive Management of Computer Resources in the Academic Health Center. Washington, D.C., Association of Academic Health Centers, 1984.

* Matheson, N.W. and J.A.D. Cooper, Academic Information Management in the Academic Health Sciences Center. Journal of Medical Education, 1982; 57(10): Part 2.

essential that medical centers use these technologies effectively in carrying out their mission. To bring about an integrated academic health sciences information center based on a network of interactive systems within a medical center will require careful planning and resources allocation and the education and retraining of present faculty and staff. The extraordinary speed with which society has assimilated newer information technologies points to the need to make rapid progress in this area in the health sciences.

- Lister Hill National Center for Biomedical Communications

The Lister Hill National Center for Biomedical Communications program of research will continue to focus on basic issues in information creation, processing and use. Major projects in automatic classification and retrieval, in bibliometrics, and in human factors in biomedical information transfer will continue. Programs in natural language processing will focus more rigorously on decision analysis problems. Experimental engineering and information sciences research will emphasize projects that have wide scope and meet the special needs of the biomedical communications community.

New efforts will be made to develop and refine new tools for knowledge dissemination and expert systems. The technologies used will include interactive videodisc, computer-based simulation, computer-assisted instruction, microcomputer based decision support systems and artificial intelligence protocols. Special efforts will concentrate on Technological Innovations in Medical Education (TIME) research.

The technologies involving videodiscs and microprocessors and flexible input devices seems finally to offer the fulfillment of the heretofore elusive promises of computer aided-instruction (CAI). This new wave of CAI technologies support sophisticated, problem-based educational paradigms which are relevant to situations of the real world. The TIME project will create a series of computer-based simulations of the clinical encounter to demonstrate innovative and effective use of these technologies in medical education. Each simulation will address problems encountered in specific stages of medical education (i.e., admissions, basic sciences, clinical sciences and practice). These prototypical simulations will be designed to demonstrate learner-centered clinical decision making and contextual problem solving through the use of these new technologies.

Over the past decade NLM has been a prime mover in supporting the development of expert systems in biomedical science. Many research problems remain which will require increasing research collaboration between the NIH and academic centers. The problems to be addressed include better knowledge representation and diagnostic algorithms, and better understanding of causal and temporal reasoning.

While the LHCBC had made substantial progress in experimental systems development over a wide spectrum of activities, greater focus on the areas of CAI and expert systems is essential to consolidate the gains made so far. It is critical that LHCBC utilize its computer-based instruction background and knowledge and its considerable technological resources to develop and document methods for effectively using the new technology to integrate state-of-thinking educational theory with state-of-the-art technology. During that process, LHCBC must bring together the experienced, knowledgeable people in the CAI field in order to avoid excessive, expensive, educational trial and error approaches which so characterized earlier CAI developments. Expert systems employing artificial intelligence techniques require intensive, long-term commitment of human and technical resources. The LHCBC is uniquely placed to catalyze and coordinate medical informatics research and development.

- National Library of Medicine Basic Library Services

The purpose of the National Library of Medicine, as defined by statute, is to assist the advancement of medical and related sciences and to aid the dissemination and exchange of information important to the progress of medicine and the public health. The Library's basic services support this mission through acquisition and preservation of the world's biomedical literature; organization of this literature by cataloging, indexing, and bibliographical listing; dissemination of the authoritative bibliographic data produced in publication and other formats; delivery of needed documents from the National Library of Medicine collection through loan or copying techniques; provision of reference and research assistance to health sciences professionals; and coordination of a national network of health sciences libraries to improve biomedical information services throughout the U.S.

NLM acquires about 16,000 new books and audiovisual programs annually and receives about 128,000 issues of some 23,000 serial publications. The Library binds about 30,000 volumes each year. As a result of these acquisitions, 16,000 cataloging records and 284,000 indexed citations are produced annually, using the Medical Subject Headings, a specialized thesaurus developed and maintained by NLM, and the National Library of Medicine Classification, a scheme for organizing books on library shelves according to biomedical subject content. These cataloging records and indexed citations are distributed in over 75 publications including Index Medicus, made available for on-line searching to about 2,300 U. S. institutions which have access to the MEDLARS system, and are distributed in machine readable form to numerous outside institutions, which in turn make them available in a variety of formats.

Each year NLM receives over 140,000 requests from other libraries for loans or copies of materials in the NLM collection. The approximately 22,000 people who come to the Library each year submit about 197,000 requests for materials not shelved in the public reading

rooms. NLM provides information in response to about 81,000 reference inquiries each year and distributes 75,000 copies of special bibliographies prepared on current topics of wide interest. The Regional Medical Library network administered by NLM processes an additional 2,000,000 document requests annually.

While the NLM's goals for its basic library services remain relatively constant from year to year, the technologies for improving the efficient and effective management of these services continue to expand in power and performance. Essential services require the NLM:

- To identify, acquire, and process rapidly new and retrospective materials to support the Library's mission.
- To store, bind, and otherwise preserve materials in the NLM collection to ensure their present and future availability to the biomedical community.
- To create and disseminate widely authoritative cataloging and indexing records for currently received literature.
- To maintain a thesaurus of subject terms and a classification scheme used by NLM and external institutions to provide optimum subject access to the biomedical literature for health sciences professionals.
- To provide rapid and effective document delivery service for inter-library loan requests which cannot be filled by the collections of other U.S. libraries and for health professionals and students who come to the NLM facility.
- To give effective reference service and research assistance to on-site users and remote users who cannot be helped by local health sciences libraries.
- To maintain an effective network of health sciences libraries in order to improve the quality and speed of biomedical information services to all U.S. health sciences professionals, regardless of their geographic location.

Basic library services are functions assigned to NLM by the National Library of Medicine Act. These services save the total biomedical library community several million dollars in staff time annually; allow local biomedical libraries to limit their collections to materials routinely needed by practitioners, educators, students, and researchers who use their facilities; and equalize access to biomedical information throughout the United States.

Some of these services are threatened by obsolescence in materials and tools. Therefore, activities to preserve the library's deteriorating collections and expand its computing power are critical. These activities include use of new technologies such as chemical mass deacidification and electronic optical disk microfilm storage. More

powerful support computers are needed to improve linkages with the private sector and online services to the research and library communities.

- MEDLARS III

The third generation of NLM's Medical Literature Analysis and Retrieval System is known as MEDLARS III. MEDLARS III is intended to (1) improve the library's processing of the medical literature by integrating the ordering, receiving, cataloging, and indexing activities under a single automated system; and (2) provide for a cost-efficient, rapid document delivery capability through the automation of an interlibrary loan routing and document location system throughout the Regional Medical Library network.

The specifications for MEDLARS III call for the creation of a totally integrated system to provide the capabilities described above. To our knowledge, the level of integration called for in these specifications is unprecedented for the size of data bases and scope of bibliographic processing activities that exist at NLM. To achieve this level of integration will require research at the leading edge of computer technology.

The principal area of research must deal with the coexistence of high-speed information retrieval activities with efficient real-time data base creation and update activities under a single data base management system. No commercially available data base management system is known that can provide this efficient combination of retrieval and update activities, therefore, significant development will be required to create a new data base technology or to modify existing data base technology. To provide this requirement, this will include research into data base machines and distributed processing.

Another important area of research in MEDLARS III will be that dealing with the provision of more timely and useful information at local levels. Research will be required into the feasibility of using relatively new technologies such as microprocessors and video/optical disks in support of this activity.

The MEDLARS II system, and other systems in place at NLM, are now over nine years old. While the volume of material that NLM must process is ever-increasing, the capabilities of these systems has not kept pace with this increased workload. They are not adaptable to real-time processing, a necessary condition to make any real improvement in processing efficiency. Further these systems are not integrated, and in many cases multiple creation of the same document is necessary in order to complete its processing.

In the area of network processing, NLM has made little improvement in automating its information retrieval system for these nine years. Interlibrary loan document delivery has remained as a 95 percent

manual activity. Automation of this important function must be realized now in order to continue to serve the medical library community.

- Specialized Information Services

The Toxicology Data Bank (TDB) aggregates factual information reported in the scientific literature relating to human and nonhuman toxicities of chemical substances. The scope and coverage of this data base has expanded to meet the requirements of hazardous waste information activities under the Superfund Act of 1980. Information and data are collected, formally reviewed by a body of experts (TDB Peer Review Committee), and then made available for online interactive use. The Remote Data Entry System (RDES) builds and maintains records, while computer conferencing and electronic mail are used for peer review.

Hazardous substances emergency response teams (operated by CDC and EPA) have indicated a frequent need for information about the identity and physical, biological, and environmental properties of chemicals that become involved in emergencies. In emergencies involving accidental chemical spills or chemical disposal sites ("chemical dumps"), action decisions are based on many factors such as (1) the chemicals involved, (2) other situation aspects such as fire or threat of fire, and (3) possible hazards to people, environmental pollution, etc. Such information is usually required quickly, at any time of the day or night, seven days a week. Vagaries in communications systems that can interfere with information retrieval from central online systems are not acceptable in these situations. The enhanced TDB represents probably the best data base for the required subject areas. Microcomputer workstations at regional offices or in response vehicles of local hazard response teams could be equipped with TDB subsets based on compounds or compound classes and employ "expert system" software to assist decision-making. Such work stations would supply support not currently available in the field.

Mobile emergency response teams, made up of health and environmental experts, who can come to the aid of local forces, have been organized by Federal and State agencies. These agencies have started to develop standard procedures to deal with emergency situations in order to minimize harm to populations, property, and the environment. The proposed research would consider the feasibility and practicability of "knowledge mining" techniques (Science, 223, No. 4642, p. 1281, 1984) for in-depth interviews of people now involved in responding to chemical emergencies, to develop a "database" of procedures, which, coupled with the NLM TDB describing chemicals and their properties would lead to a set of heuristics ("If this describes the situation, then consider doing such and such") that could be incorporated in an Expert System for chemical emergency response. Additionally, suitable search systems to access subsets of the TDB on-site need development. This response system needs to be adapted to standard microcomputer operating systems (e.g., CP/M, MSDOS), and existing

data base management software (e.g. dBASE II, Sci-Mate). The software must be "user friendly" because these users will not be sophisticated or experienced in computer searching and the system often will be accessed under high pressure, emergency conditions.

The importance of a successful implementation of such a system is obvious. It could help to save lives, reduce injuries and limit damage to property and the environment. Even a partial success might lead to computerized "checklists" of emergency response actions to be taken in certain circumstances. Another outcome of such a project could be a codified, well-structured list of what experts actually do in various emergencies that might be useful in training of emergency response personnel. To our knowledge, no other effort to develop such an Expert System is now taking place at the Federal level. Finding alternative methods of distributing information is a critical feature of all NLM programs. Local storage and retrieval of scientific information utilizing microcomputers and optical video disk technologies is an imperative.

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Areas of Opportunity

- Macromolecular Graphics System

The growing scientific comprehension that undergirds the conduct of modern medicine i.e., medicine research, medical care and medicine education stems directly from an improved understanding of the details of life processes. The computer in one or another of its many sizes has emerged as a uniquely powerful tool in the scientific process that is creating and conveying this understanding.

Over the last decade at NIH and a few other leading research centers, computer systems were developed to transform voluminous and complex numerical descriptions of large biological molecules (macromolecules) into dynamic three dimensional images (graphics). This technique allows scientists at NIH to see and explore interactively the structure of proteins and nucleic acids in a range of detail from atoms to multimolecular subunits. Extensive, productive research has come from the existing NIH molecular graphics system built by the DCRT. The challenge is to extend this work by designing and applying newer hardware/software systems.

Previous work shows that it is possible to use molecular graphics techniques for creation of valid images of known macromolecules and perhaps some that do not exist in nature. But the time required on the available systems to compute the minimal energy configuration of new molecules can be very lengthy (hours or even days). Because of recent advances in computer technology the opportunity now exists to build a new hardware/software system that will create and validate configurations of new molecules in a reasonable time frame (seconds or minutes) and display them in ways that are more useful to scientists.

This work requires high priority for additional funding because it is an essential complement to the new technology that has emerged over the last five years for physically modifying or creating biological macromolecules (molecular engineering using recombinant and synthetic DNA techniques). The ability to conceive, construct, conformationally validate and examine images of new molecules provides a powerful and efficient way to guide decisions about physically creating modified or new enzymes, antibodies, nucleic acids, etc.

It is also clear that the new computer system can be used to model graphically viruses, membranes and other subcellular structures. At this level it will complement other computing techniques being developed and used at NIH to analyze images of such structures obtained from electron microscopes.

- Selection and Installation of a New Data Base Management System for the Central Computing Facility

New developments in data base management technology have created systems easier to use than the one currently in existence at the NIH. To prepare for the future needs in this area for NIH, DCRT must begin a search and evaluation project to select a new data base system that will be required to meet NIH's administrative and scientific needs.

Data base management will be the future direction for computer applications of all types. One central data base can meet the needs of a diverse community of users negating the need for numerous specific applications using the same set of data elements. In light of dwindling resources the use of a data base management system can result in savings of manpower and dollars.

- Personal Workstation Project That is Assessing the Use of Personal Computers in the Office, Laboratory, and Clinic

The power, speed, and simplicity of the personal computer brings to the desk and laboratory bench computing capability for individuals that never existed in the past. As future technological developments increase this power and speed the need for large central computer power will be reduced for certain types of applications. However, after computing is done at the local level the need to communicate results to the central facility for processing will still be needed. The Personal Workstation Project is evaluating all of these requirements for the NIH.

The growth of use of personal computers in the BID's has created overwhelming demand for DCRT to take the lead in the application of personal computers to scientific and administrative problems. In order to meet this demand DCRT was required to initiate this project as a high priority project. By 1986 additional resources will be required to keep abreast of the state-of-the-art and the need for continued growth of applications in this area.

- Reprogramming of a Major Bio-mathematical Modeling Software Package (MLAB)

MLAB is a software package developed at NIH for computer analysis of mathematical models and generation of graphical displays. It was designed for easy use by biomedical scientists who may have little previous experience with computers. It has been used by hundreds of intramural scientists at NIH, and by many extramural scientists through the PROPHET system or through export to other computer installations.

The current version of MLAB is about 25000 lines of code in a high-level language available only for DEC-10 and DEC-20 computers. In order to make MLAB more widely available and avoid dependence on a single computer vendor, it is proposed to redesign and rewrite MLAB in a portable form, usable on many different computers of all sizes.

- Develop System to Create, Archive, Transmit, and Display Images from CAT Scans and NMP/PETT Images

A Picture Archiving and Communication System (PACS) is one which will automate the storage and transmission of medical images in the Clinical Center (CC). The system will serve the departments which generate images, including Radiology, Nuclear Medicine, and Radiation Oncology, and will also make images quickly available to operating rooms, nursing stations, and physicians' offices throughout the CC.

The backbone of a PACS is the network architecture, which will allow data-intensive image files to be rapidly transmitted from one location to another. Nodes which transmit and receive data will be placed at imaging devices, data management and storage devices, and viewing stations. Currently available network transmission media include baseband coaxial cable, broadband coaxial cable, and fiber optics.

A strategy involving two major storage facilities will likely be implemented. A short term facility, consisting of high speed magnetic disks, will hold images for four to six weeks, the period of maximum image use. Long term storage will be performed with laser disks, a non-eraseable medium which can hold thousands of images on a single platter. Laser disk "juke boxes", still under development, will allow on-line access to over a year's worth of images.

The system will consist of state-of-the-art mass storage devices, which will be able to keep several week's worth of data available for immediate viewing, as well as the most advanced network communication, data management, and image display equipment. When in place, the system will allow the storage of images from several modalities in a central facility and will enable physicians to view those images from a variety of locations.

A sophisticated data management scheme will keep track of the images and allow researchers to group them by patient, modality, or disease, thus facilitating the longitudinal and population studies so essential to productive medical research.

